Neurology

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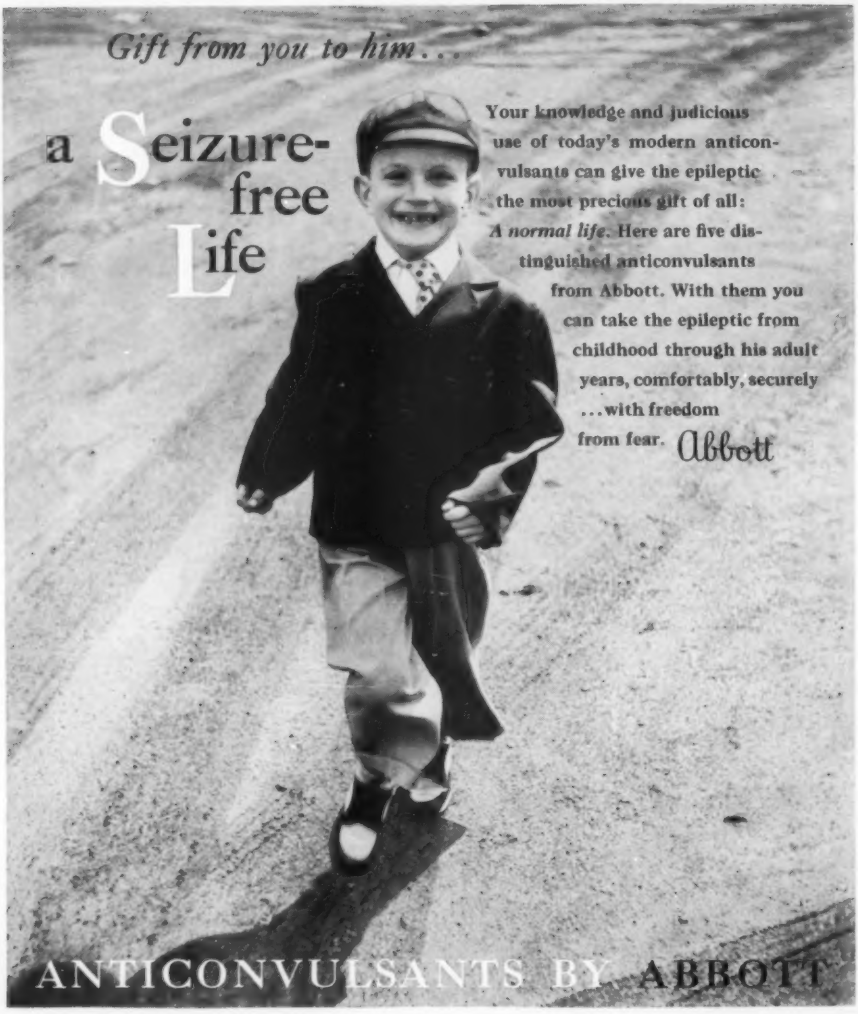
THE AMERICAN ACADEMY OF NEUROLOGY

JANUARY—1958
Volume 8 — Number 1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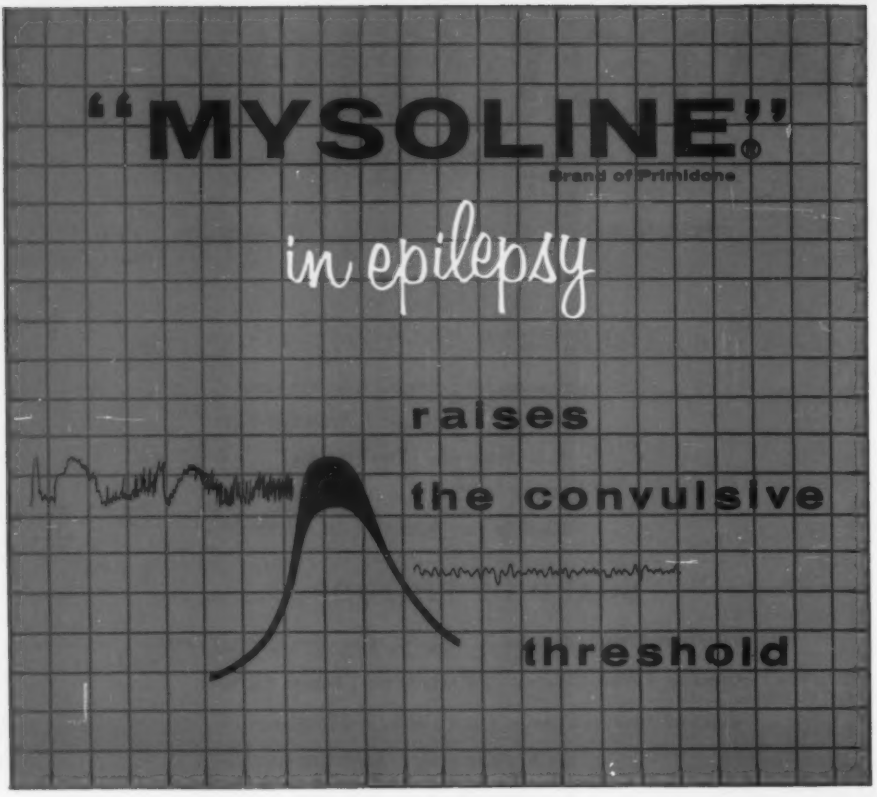

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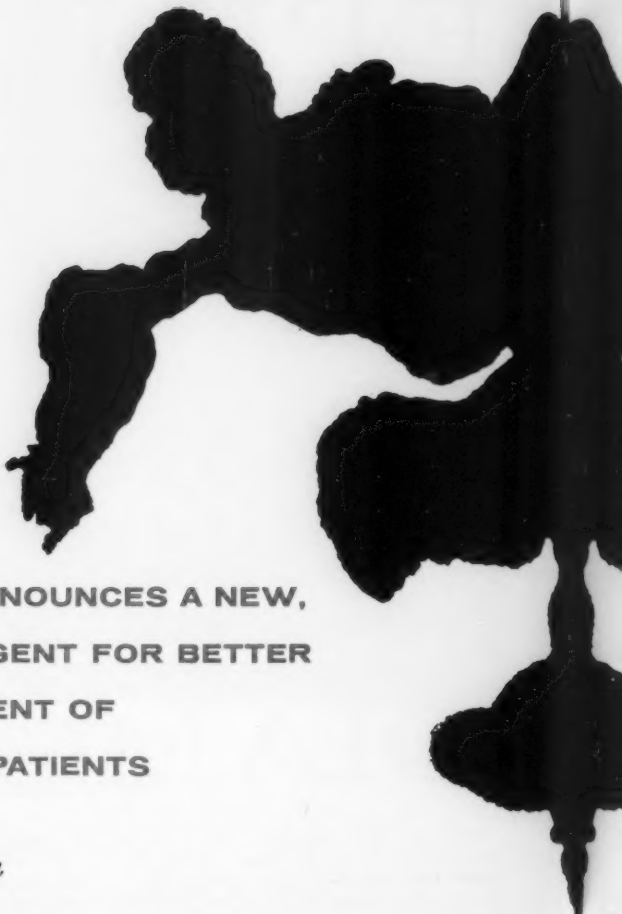

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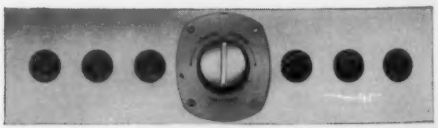

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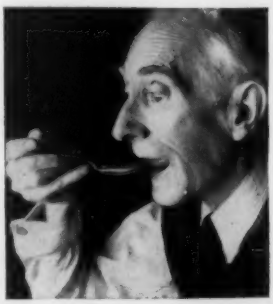

Above and right are action pictures, taken from a Warner-Chilcott film study, of a parkinsonian patient before and after initiation of Parsidol therapy for major tremor.

Neurology Volume 8 • Number 1

Brainstem Tumors in Children

Patrick F. Bray, M.D., Sidney Carter, M.D. and Juan M. Taveras, M.D.*

TUMORS ARISING within the brainstem are more common in children than in adults. The onset of neurologic symptoms and signs is frequently insidious and increased intracranial pressure usually does not develop until late in the course of the disease, if at all. This slowly developing clinical picture and the wide range of neurologic signs frequently make early diagnosis difficult. The multiplicity and diversity of the neurologic signs may mislead one into thinking first of primary infections of the central nervous system, postinfectious encephalopathies, demyelinating processes, cerebrovascular accidents, and congenital brain defects, including the all-inclusive concept of cerebral palsy.

There were 12 brainstem gliomas in the 100 unselected autopsy-verified cases of intracranial tumor reported by Bailey, Buchanan, and Bucy.[1] Walker and Hopple,[2] in reviewing the same number of cases (100), also reported 12 instances of pontine tumor verified by tissue examination or operative visualization. Again in 100 cases, Smith and Fincher[3] reported an incidence of five pontine neoplasms. Ingraham and Matson[4] reported 30 cases in their series of 313 brain tumors in children, 23 of which had the diagnosis confirmed at operation or autopsy. Out of 85 verified cases collected by Cuneo and Rand,[5] there were two pontine tumors. In reporting 427 cases of brain tumor in children, Keith, Craig, and Kernohan[6] described them in terms of pathologic type and position in relation to the tentorium, but did not break down the group further as to tumor location.

It is the purpose of this paper to document the pattern of neurologic symptoms and signs in this disease and to re-emphasize the important diagnostic role of pneumoencephalography. More important probably than either of these objectives is the need to point out that the use of roentgen therapy in this relatively hopeless group can offer temporary improvement and, in some instances, a prolonged survival.

CASE MATERIAL

We have collected 48 cases with the diagnosis of brainstem tumor which were seen over the last 24 years at the Neurological Institute and Babies Hospital of the Columbia-Presbyterian Medical Center in New York City. All of these children had the onset of their illness before their sixteenth birthday.

The criteria upon which the diagnosis was based are illustrated in figure 1. The relatively low rate of histologic confirmation in this study is due to the fact that, when the clinical signs and diagnostic x-ray contrast studies were conclusive, operative intervention was not carried out. Many of the patients died at home after roentgen therapy. Also, tissue diagnosis was uncommon, even in those cases confirmed by surgical exploration, because the close involvement of this tumor in the brainstem renders it a hazardous area to biopsy.

The tumors in ten of the cases were verified at autopsy and varied in their histologic structure. Five cases showed varying degrees of glioblastomatous change arising from an astrocytoma. Three tumors were classified as astrocytoma and two as spongioblastoma polare. This variability in the microscopic picture is in

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keeping with the experience of others,[1,4] and has been cause for considerable controversy among pathologists striving for a correct and uniform terminology.

Diagnostic confirmation in six cases was made by exploration of the posterior fossa and visualization of the brainstem. Three of these patients were explored surgically on the basis of air contrast studies which had been thought to indicate a cerebellar tumor. The presence of papilledema prompted surgery in the other three patients, despite neurologic signs which favored the diagnosis of a brainstem lesion. In all six the surgeons noted intrinsic enlargement of the pons or medulla by tumor mass. In the three cases in which biopsy was performed, a tissue diagnosis of astrocytoma was made in two and in the third case the tissue removed was insufficient for diagnosis.

Thirty-five patients had air contrast studies which were technically satisfactory. Thirty-two of these revealed abnormalities which were considered typical of brainstem tumor, and eight of the 32 cases were proved at autopsy. All but two of the 24 cases which were not verified by postmortem study showed neurologic abnormalities which were clinically typical. Three cases in the total of 35 air contrast studies revealed findings that were erroneous or not diagnostic. However, in all three of these patients the diagnosis was later made by suboccipital exploration and visualization of the tumor.

Eight cases have been included in this series in which there was neither histopathologic nor radiologic evidence to support the diagnosis, but in which the clinical picture was typical. The typical clinical picture of brainstem glioma has been described by many authors.[1,4,7] Their data, in addition to an analysis of our other 40 cases in which confirmatory evidence was available, serve as reference in support of the diagnosis. Among these eight cases, seven patients were known to have died, the longest survival period being 14 months. This period of limited longevity is circumstantial evidence in keeping with the clinical evidence of brainstem glioma.

ANALYSIS OF CASE MATERIAL

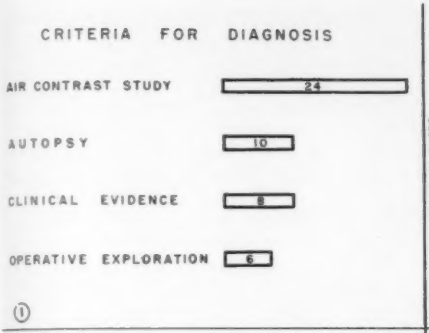
Race and sex. The data on race and sex distribution of these 48 patients with brainstem tumor are recorded in figure 2. There were 23 males and 25 females. In terms of race distribution there were 41 white children (85 per cent); seven of the patients (15 per cent) were colored. These latter figures are in keeping with the average distribution for race in the greater New York area.

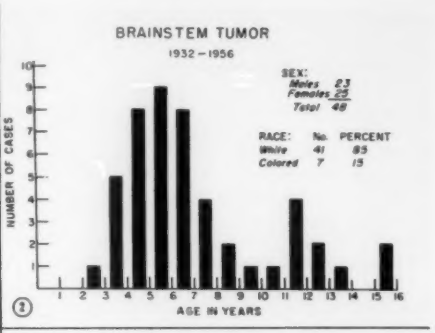
Age of onset. The average age at the onset of symptoms in this series of cases varied from two to 16 years, with an average of six years and eight months (figure 2). This figure corresponds closely to that of the 30 cases reported by Ingraham and Matson.[4] In only one case was the age at onset of symptoms under three years of age. This is in contrast to the experience with medulloblastoma where the peak incidence occurred at about three years of age in the 68 such tumors reported by Ingraham and Matson.[4] The age of six years and eight months does not help by itself to distinguish brainstem gliomas from other commonly occurring posterior fossa mass lesions like cerebellar astrocytoma and ependymoma.

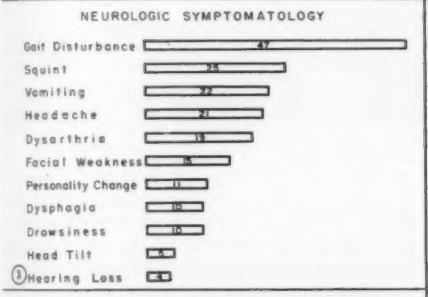
Symptomatology. The incidence of symptoms is recorded in figure 3. It is frequently impossible to differentiate historically whether gait disturbance is a sign of weakness due to corticospinal tract involvement or a sign of ataxia due to a cerebellar pathway lesion. A little over half the patients were reported to have a squint, and slightly less than half had vomiting, headache, and speech disturbance. To account for the common early symptoms of headache and vomiting is difficult since in the majority of cases it is unlikely that they are a reflection of increased intracranial pressure. It has been suggested by some that vomiting may be due to direct involvement of the medullary vomiting center. On the other hand, these symptoms may be nonspecific. By the time these youngsters were first hospitalized, personality changes, swallowing difficulties, and drowsiness were noted in approximately 25 per cent of the cases.

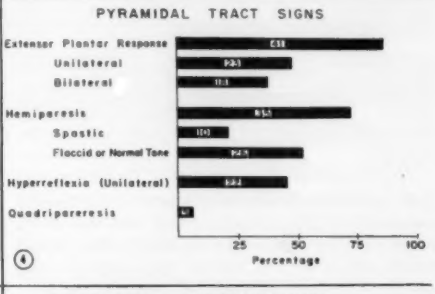
Incidence of neurologic signs. It is apparent from figure 4 that pyramidal tract signs are very common in patients with brainstem glioma. Hemiparesis associated with a reflex preponderance and Babinski sign is the usual picture. Frequently bilateral reflex changes and occasionally quadriparesis were seen, indicating bilateral pyramidal tract involvement.

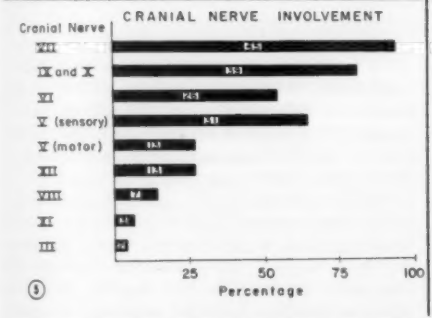
Involvement of multiple cranial nerve nuclei is also the rule in these children (figure 5). The most commonly involved cranial nerve in this series was the seventh, and 25 per cent of all patients showed a facial diplegia at some time during their disease. Ninth and tenth nerve involvement occurred often, accounting for the common symptoms of dysarthria and dysphagia. Sensory fifth involvement was seen frequently, whereas the motor branch











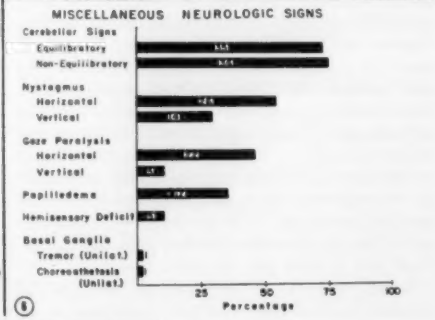


FIG. 1. Criteria for diagnostic grouping of 48 patients with brainstem tumor.
FIG. 2. Age, sex, and race distribution in series of 48 children with brainstem tumor.
FIG. 3. Incidence of neurologic symptoms in 48 children with brainstem tumor.
FIG. 4. Incidence of pyramidal tract signs in 48 children with brainstem tumor.
FIG. 5. Incidence of cranial nerve signs in 48 cases of brainstem tumor.
FIG. 6. Incidence of miscellaneous neurologic signs in 48 children with brainstem tumor.

of this nerve seemed to suffer less often, particularly in the latter stages of the disease. Sixth nerve palsy was noted in a little over half the cases. The tongue was involved in about a fourth, and deafness, usually unilateral, occurred in seven patients. Other neurologic signs seen in this group are charted in figure 6. Both equilibratory and non-equilibratory ataxia were found in the majority of these patients. This has been interpreted to indicate involvement of the corticopontocerebellar fibers, the so-called middle cerebellar peduncle as it courses through the stem.

Horizontal nystagmus was seen in over half the patients, and vertical nystagmus in 29 per cent. The critical finding of gaze paralysis was present in almost half the cases at some time and was felt to be most important in localizing the lesion inside the brainstem. Upward gaze paralysis, which was noted in five

patients, is regarded as a cardinal sign of upper midbrain compression, and for this reason pinealoma was considered in the differential diagnosis of these cases. As pointed out by other authors, sensory deficits are uncommon with tumors of the stem since the medial lemniscus seems to be peculiarly resistant to the effects of pressure. Only five patients (10 per cent) in this series demonstrated a hemisensory deficit at some time during their illness. Only two patients had involuntary movements indicating involvement of the basal ganglia.

In this group of 48 patients, 17, or 35 per cent, developed papilledema at some time during their illness. The average interval between the onset of symptoms and the development of papilledema was five months. Among the 31 children who were not observed to develop papilledema, an average interval of four months elapsed between the onset of symptoms and the last negative eye ground examination.

Cerebrospinal fluid findings. Cerebrospinal fluid pressure measurements were recorded in ten patients; the average value was 155 mm. of water. Only two of these patients had values which could be considered even slightly elevated (200 and 220 mm. of water). Twenty-one patients had cerebrospinal fluid protein determinations. The average value in 20 of these 21 patients was 28 mg. per 100 ml. The only patient who had an elevated protein determination, 68 mg. per 100 ml., was also the only one who had a significant elevation in his cell count, 207 cells per cu. mm. At autopsy he was found to have a glioblastoma arising in an astrocytoma which had extended to involve the leptomeninges. The average cell count in ten of the 11 patients who had cell determinations was 5 cells per cu. mm.

Roentgenographic findings. A total of 34 patients had simple roentgen examination of the skull. Evidence of increased intracranial pressure was found in seven of these 34 cases (five of the seven manifested by suture separation and two by changes in the sella turcica).

In figure 7 comparative lateral view pneumoencephalograms are shown in a normal child and in a child with a brainstem tumor. The typical findings on pneumoencephalography in cases of brainstem tumor include posterior and upward displacement of the aqueduct of Sylvius and the fourth ventricle ("bowing" of the aqueduct), as seen in the lateral roentgenogram. In this same view the anterior margin of the fourth ventricle is sharply defined and the cisterna pontis may be narrowed. In cases where the tumor is quite large, one may see elevation of the floor of the posterior part of the third ventricle (figure 7). Thirty of the 48 cases being reviewed had air contrast examinations in which the size of the lateral or the third ventricle could be estimated. Ventricular dilatation was present in 20 of these 30 patients, but the degree of ventricular enlargement was most frequently slight or moderate, even in patients with large tumors.

Results of radiotherapy. In this group of 48 brainstem tumors, 39 patients lived long enough to receive at least one course of radiotherapy. In the cases treated prior to 1952 the patients received approximate tumor doses of 1,000 to 1,200 r over a period of 12 to 30 days, depending upon the condition of the patient. This dose was repeated two or three times at six-week intervals. In the past four years an effort has been made to deliver a single tumor dose to an adult of 4,000 r in 28 days and this is scaled down for children. In infants under two years of age, half of the adult dose is given; between three and four years of age, 75 per cent of the adult dose is used; the dose is increased gradually with increasing age until at eight years the full adult tumor dose is employed.

For purposes of discussion we have divided the cases into three groups: 1) those followed until death (24 cases); 2) those still alive one month to 13 years after treatment (eight cases); 3) those lost to follow-up after a period of observation ranging from one month to three years (seven cases).

The 24 patients in the first group received one or more courses of roentgen therapy. Survival time in these patients was computed from the first hospital admission date, when the diagnosis was established, to the date of death. The average survival time among this group was nine months. Fifteen of the 24 cases (63 per cent) were thought to have shown clinical improvement following treatment. If one compares the survival time in these 15 patients responding favorably to roentgen therapy with those nine failing to benefit, one finds average survival times of 11 and one-fourth months and four and three-fourth months, respectively.

There was a striking consistency in the time that it took for clinical improvement to appear. With the first course of therapy, practically all patients manifested improvement between three and six weeks after the onset of treatment. We have been interested in document-

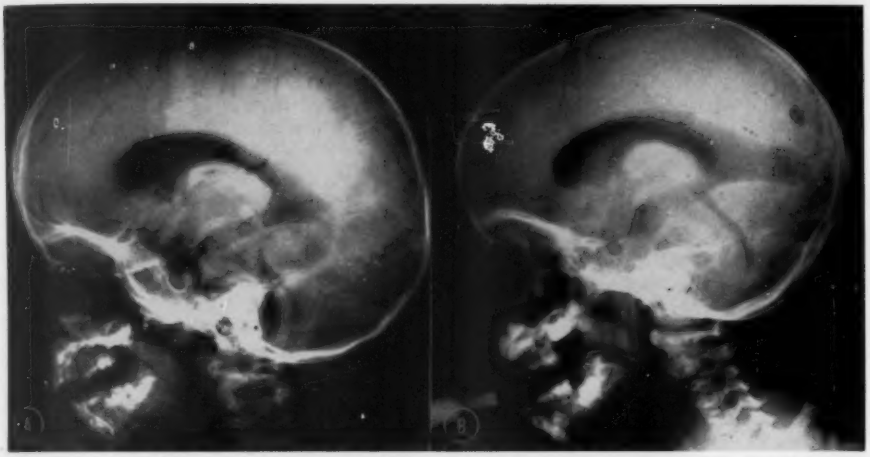


FIG. 7. Normal air study (left) compared with that seen in a patient with a large brainstem tumor (right). Posterior and upward displacement of the aqueduct and fourth ventricle is seen.

ing, if possible, the pattern of clinical improvement; this could be done from the available data in 13 patients. Ten of the children showed incomplete clearing of the cranial nerve signs, nine manifested partial disappearance of corticospinal tract signs, and six demonstrated improvement in such nonspecific ways as the development of a sense of well-being and clearing of headache and vomiting.

Among the 15 patients who showed clinical improvement in response to the initial roentgen course, 12 received a second course of therapy. Seven of these were believed to show some of the signs of clinical improvement when they were re-treated. The time interval and the pattern of improvement did not differ appreciably from those following the first course of treatment. There were no children in this group of patients followed to death who responded to subsequent courses of therapy after failing to respond to the initial treatment series.

There are eight patients in our second group who are still alive after having received roentgen therapy. Naturally, those individuals with the longest survival times would fall into this group.

The third group of patients who received roentgen therapy were those in whom no follow-up was available at the time of writing; there were seven patients in this group. Six of them were seen over a sufficiently long time so that their response to therapy could be evaluated. Four of the six appeared to have had at least one beneficial response. The follow-up periods and clinical observations were inadequate to evaluate subsequent courses of therapy in the three individuals who received them.

In an effort to predetermine those individuals who would respond favorably to radiotherapy, the clinical findings have been compared in those who did and those who did not show improvement following treatment. There was no striking difference in the age at onset of symptoms (seven years and six months, as compared with seven years and five months). Likewise, there appears to be no real difference between the groups in the duration of symptoms prior to the first hospital admission (2.8 months, compared with 2.4 months). The

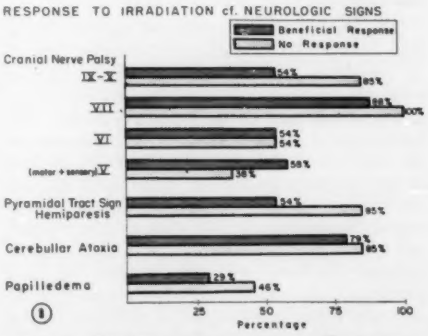


FIG. 8. Correlation between response to radiation therapy and the presence of neurologic signs.

neurologic findings used for comparison were those present at the time of first hospital admission. The two groups appeared to differ appreciably (figure 8) in terms of the degree of pyramidal tract involvement, the incidence of tenth cranial nerve dysfunction, and possibly in the incidence of papilledema. Inspection of the data reveals that there is apparently no significant difference in the incidence of other cranial nerve involvement or cerebellar signs. In general, the severity of neurologic involvement was greater in the group failing to respond to treatment. As one might expect, complications of tenth nerve dysfunction were frequent forerunners of the terminal state in this group of patients and this may have been a factor affecting the difference of survival times in the two groups.

In summary, 37 patients received at least one course of radiation therapy. They survived and were followed long enough to permit clinical evaluation. Twenty-four of these cases showed definite improvement in neurologic signs for a variable period of time, and three patients were alive four, six, and 13 years after radiotherapy.

Nine patients received no radiotherapy, usually because they died so early after admission that treatment could not be instituted. Seven of the nine patients succumbed during the first hospital admission, with eight of the nine dying within a six-week period. Three of these nine patients were explored surgically because of inconclusive clinical or roentgenographic findings and all three patients died within eight days of being admitted to the hospital. The clinical picture in this group did not differ appreciably from that seen in the treated patients.

DISCUSSION

Recognition of the advanced case of brainstem tumor should present no serious difficulty, providing the physician becomes familiar with the findings produced by an expanding lesion in this part of the nervous system. The neurologic abnormalities have been documented quite adequately by others, and the analysis of the findings in our 48 cases does not necessitate any serious changes in diagnostic concepts. Symptoms of gait disturbance, squint, and dysarthria were seen commonly in our experience, as they were with others. The fully developed picture of the patient with pyramidal tract signs, involvement of multiple cranial nerve nuclei, and cerebellar ataxia usually makes itself recognized quickly as a progressive disease of the central nervous system. The patient with the insidiously developing picture, however, may go unrecognized for some time. One unfortunate patient who presented with a strabismus was treated with eye muscle surgery, and this same child later had his tonsils removed when he developed dysarthria.

In our series both the seventh and tenth cranial nerves were involved more commonly than the sixth. This is in contrast to the experience of both Ingraham and Matson[4] and Bucy[8] who found the sixth cranial nerve to be affected most commonly. Also noteworthy is the fact that seven patients had either unilateral or bilateral deafness, something not emphasized by others. Our experience in finding sensory deficits infrequently was in keeping with that of Ford.[7]

The problem of increased intracranial pressure has been considered at some length in the analysis of these cases. We discovered some degree of ventricular dilatation in two-thirds of the patients who had air contrast examinations. This is in contrast to the observed incidence of papilledema. These figures tend to support the idea that, although one is frequently dealing with an obstructive lesion, the obstruction is undoubtedly slow in its development. Lumbar puncture with pressure recording was carried out in only a limited number of patients for several reasons. The potential danger of lumbar tap in a patient with a posterior fossa mass lesion has long been a deterring factor. Also it has been felt that air contrast study would yield more definitive diagnostic data and avoid delay. After recent years' experience, however, the feeling has developed among this group that considerable data can be safely obtained from pressure recordings, cell count, and protein determinations. However, it must be emphasized that before spinal tap is carried out, judicious selection of those patients who present with neurologic signs common to this group of patients is essential.

The cerebrospinal fluid formula in this series was almost uniformly normal, both in terms of cellular elements and protein content. Only two out of ten patients showed an elevation of initial pressure on lumbar puncture. The finding of an abnormal fluid, therefore, would suggest a process other than brainstem tumor.

The accurate diagnostic role of pneumoencephalography has already been emphasized. It is apparent that this technic is preferable to ventriculography in these patients, since not

only can small amounts of gas be used (10 to 30 cc. of air), but the contrast medium is more likely to reach the areas where it is critical for diagnosis, the fourth ventricle, aqueduct, and basal cisterns. In fact, 10 or 20 cc. of air can be injected without the removal of any spinal fluid and this further decreases the morbidity of the procedure.

The management of patients with this disorder is a challenging and generally discouraging matter. Surgery has little to offer, although posterior fossa decompressions and shunting procedures to relieve intracranial hypertension have been used as palliative measures in selected cases. If one refers to the experience of others, it bcomes apparent that radiotherapy has not been used with much enthusiasm. Ingraham and Matson[4] have the impression that occasionally symptoms are relieved temporarily and they recommend a tumor dose of 3,000 r. Peirce and co-workers[9] reported definite clinical improvement with roentgen therapy but they did not specifically differentiate the response of their brainstem cases in describing their series of 80 patients with all types of brain tumor. In another report by Peirce and Bouchard[10] the treatment of 243 brain tumors is reviewed, and again they point out the major role to be played by radiation therapy in management, although it was not entirely clear how many brainstem tumors were treated and whether their response was different from that of other cerebral neoplasms. The one case of brainstem tumor in the series of Freid and Davidoff[11] was not influenced by roentgen therapy. Our experience with radiation therapy has certainly not been dramatic. However, the repeated experience of having induced a clear-cut remission of neurologic symptoms and signs for a short period of time deserves emphasis. The majority of those patients who received a complete course of treatment were thought to have shown improvement with radiation therapy. It should be emphasized that there is a lag period, usually three to six weeks, between the onset of treatment and the initial signs of improvement. The signs of improvement usually noted were partial clearing of cranial nerve and pyramidal tract abnormalities. No patients responded well to subsequent courses of roentgen therapy after failing to improve with the initial series.

As to the relationship of therapeutic dose of radiation to clinical response, it has been our impression that the higher doses which we have been employing recently produce a remission of symptoms and signs in a greater percentage of patients. It is questionable whether there is any increase in survival time. Also, the recurrence of symptoms or signs seems to take place at approximately the same rate. However, a sufficiently large number of patients have not been treated in this manner, and it is not possible to state at this time whether there is such a thing as a radiocurable brainstem tumor. If any of these tumors is amenable to cure by radiation, the higher dose which still produces no damage to the uninvolved portions of the stem is to be preferred.

SUMMARY

1. The case histories of 48 patients have been reviewed in whom the diagnosis of brainstem tumor was made by autopsy examination, surgical visualization, x-ray air contrast study, or clinical evidence alone.

2. The vital statistics, symptomatology, and neurologic findings in these patients have been presented.

3. The diagnostic criteria found on air contrast study have been pointed out and their importance has been emphasized.

4. The response of a portion of this group of patients to radiation therapy has been reported. The occurrence of clinical remission in 24 of the 37 patients treated with radiotherapy has been pointed out. An attempt has been made to correlate the clinical findings with the presence or absence of a favorable response to this treatment.

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Mechanism of Production of Papilledema in the Guillain-Barré Syndrome

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THE PRESENCE of increased intracranial pressure and papilledema in cases of the Guillain-Barré syndrome (infectious polyneuritis, infectious neuronitis, encephalomyeloradiculitis) has been reported a number of times.[1–13] Judging from the paucity of such case reports, it appears that increased cerebrospinal fluid pressure and papilledema rarely occur with the Guillain-Barré syndrome or are frequently overlooked. However, the mechanism of its production when present raises points of theoretical and practical importance. Drew and Magee[9] concluded that the relationship of papilledema to the Guillain-Barré syndrome could not be explained adequately. Several investigators [10–14] have suggested that excessive protein in the spinal fluid blocks absorption of the arachnoid villi so that external hydrocephalus is produced, with increased intracranial pressure and papilledema. There are, however, certain objections to this theory. Studies of the case presented here and an analysis of reported cases suggest that another mechanism may account more accurately for increased intracranial pressure and papilledema. It is suggested that an actual increase in the brain substance due to cerebral edema may be the cause. The brain swelling in the case reported here resembles that described in cases of pseudotumor cerebri, both in its clinical and pathologic features.

CASE REPORT

An 11 year old boy entered the hospital with the complaint of weakness of the arms and legs for two and one-half weeks and double vision for two weeks.

Four weeks prior to admission, he suffered a "slight cold" accompanied by chills. Ten days following this, he noted weakness of the legs which was progressive, and he required assistance in standing and walking when hospitalized. There was numbness and aching in the calves and anterior thighs. The diplopia had been persistent since its onset. On several occasions he had difficulty swallowing. There was no disturbance of bowel or bladder control.

The initial examination revealed bilaterally symmetric weakness of the arms and legs with the greatest weakness proximally in the arms and distally in the legs. He could raise his legs only six inches from the bed and could not assume a sitting position without assistance. All tendon stretch reflexes were absent. There was symmetric diminution of sensation below the knees which was most marked for pallesthesia and position sense, less so for light touch; pain sensation was preserved. Visual acuity at the time of admission was 6/6 bilaterally. There was a diplopia on right lateral gaze, with mild weakness of the right external rectus. The right optic disk was slightly blurred. His blood pressure was 138/80, pulse 102, and temperature 99.4° F. Examination was otherwise unremarkable, except for obesity and undescended testicles.

Blood count and urinalysis were normal. Urinary lead excretion was 0.06 mg./24 hours (normal—less than 0.1 mg./24 hours). The spinal fluid contained three cells per cu. mm., Pandy reaction was 4+, and total protein was 480 mg. per cent. The pressure was not measured. Roentgenograms of the skull were interpreted as normal.

There was little change in motor or sensory deficits during the first month of observation. The patient complained of headaches and vomited on four occasions. Eleven days after admission (four weeks after onset of symptoms), it was observed that there was definite bilateral papilledema with venous congestion and hemorrhages around the disk margins. Fifteen days after admission, the disk elevation was measured at two diopters bilaterally and the visual acuity was 6/9 bilaterally. The neurologic status remained the same, he was alert, but papilledema steadily increased. Nineteen days after admission, a second lumbar puncture was performed and the initial pressure of the spinal fluid was over 500 mm. of water, there were no cells, Pandy reaction was 4+, and the total protein was 317 mg. per cent.

Ventriculography was performed on the twenty-seventh hospital day. Roentgenograms revealed normal ventricles without evidence of displacement, distortion, or dilatation (figure 1). Following this, a right subtemporal decompression and cortical biopsy of the temporal lobe were performed. The operator found the brain to be swollen, with immediate bulging through the area of opened dura. Following this, the site of decompression remained tense and bulging, but headaches did not recur.

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Three weeks after the subtemporal decompression, there was still moderate papilledema with hemorrhages, but muscle strength was improving. On his sixty-third hospital day, the optic disks were flat and the site of the decompression was still bulging 2 cm. above the surrounding tissue. The various modalities of sensation were now normal. The stretch reflexes were absent, and strength was estimated at 90 per cent of normal. He was discharged at this time.

He was re-examined nine and one-half months later (one year after the onset of his illness). He had had no headaches. The only abnormal findings at this time were bulging (noted as 3+) of the decompression site, very mild weakness of the ankle dorsiflexors, and hypoactive reflexes. Visual acuity was 6/6 bilaterally and the optic disks were flat.

The biopsy (figures 2 and 3) disclosed marked intracellular edema with occasional chromatolysis. There was no evidence of an active inflammatory process, vascular changes, or demyelination.

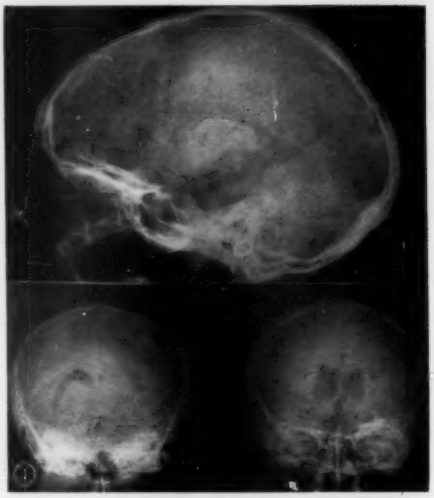

FIG. 1. Ventriculograms of case report (lateral, posteroanterior, and anteroposterior views).

DISCUSSION

In almost all of the reported cases of Guillain-Barré syndrome with papilledema, two findings are striking. There is increased cerebrospinal fluid pressure and vision, although sometimes blurred, remains largely unaltered except for enlargement of the blind spots (table 1). The preserved vision excludes the possibility of the observed optic disk abnormality being optic neuritis, a point emphasized by Drew and Magee.[9]

Several writers, as stated before, believe that any explanation for the increased cerebrospinal fluid pressure and papilledema must take into account the role of high protein levels in the cerebrospinal fluid. They advance the idea that the excessive protein blocks the absorption of cerebrospinal fluid by the arachnoid villi so that an external hydrocephalus is produced. The following points favoring this theory have been stressed by one or more of these writers: 1) cerebrospinal fluid protein is exceedingly high in those patients who have increased pressure and papilledema; 2) the increased pressure and papilledema occur late in the illness, allowing sufficient time for blockage of the absorption to take place; 3) Gardner and coworkers[14] demonstrated that the addition of autologous serum protein reduced the rate of absorption of Ringer's solution from the subarachnoid space in a dog; 4) the finding of an amorphous material presumed to be protein in the arachnoid villi in the case report by Denny-Brown;[10] 5) the similarity to those instances of increased cerebrospinal fluid pressure and papilledema occurring in spinal cord tumors,[14,15] small acoustic neurinoma,[14] and poliomyelitis[16] where there is no demonstrable block in the intracranial cerebrospinal pathway but where there is a high cerebrospinal fluid protein content; and 6) the alertness of the patient, the normal electroencephalogram, and the high Ayala index in the patient of Feldman and associates[13] which they felt was irreconcilable with the notion that cerebral edema may be the cause of increased intracranial pressure in these cases.

From the findings of several reported cases (table 1), it is apparent that while the cerebrospinal fluid protein is often exceedingly high and the rise in pressure and papilledema does often occur late in the course of the illness, this relationship is not constant. The present case report emphasizes this, in that papilledema was suspected two and one-half weeks and definitely observed four weeks after the onset of the illness. It is likely that the papilledema would be recorded much earlier in the course of this disease if the fundi were visualized at frequent intervals. It is well known that the cerebrospinal protein determination in fluid from the lumbar sac is a poor index of the protein level of the intracranial fluid. Bassoe[17] reported a case of Guillain-Barré syndrome with papilledema in which the protein content of the fluid in the lumbar sac was 2,000 mg. per cent while the cisternal fluid protein level was 25 mg. per cent.

TABLE 1

CASE REPORT	AGE	SEX	PAPILLEDEMA (Time after onset of illness)	OPTIC DISKS		VISUAL ACUITY		CSF PRESSURE mm. (H_2O)	CSF PROTEIN (mg. per cent)	CSF CELL COUNT (cells/mm.^{3})
				OD	OS	OD	OS			
Present case	11	M	4 wks.	2D	2D	6/9	6/9	500	317	0
Gilpin et al[1]	37	F		3D	3D				400	3
Gilpin et al	25	F	1 mo.	3D	2D	N	N	330	400	24
Louria & Mandelbaum[2]	16	M	15 days	H	H			110	42	8
Polan & Baker[3]	26	F	1 mo.	3D	3D	R	R	258	76.3	18
Baker[4]	39	F		C	C				58	22
Baker	26	F		C	C				109	0
Baker	29	F		C	C				243	0
Baker	37	F		C	C				18.4	1
Baker	38	M		C	C				253	11
Ford & Walsh[5]	26	F	7 mos.	3D	3D	N	N	600	470	1
Ford & Walsh	16	M	8 mos.	M	M	N	N	400	200	2
Chusid & Marquardt[6]	37	M	7 mos.	3D	3D			350	815	0
Hand & Rudoy[7]		M	4 days	B	B				310	
Hand & Rudoy	24	M	2 mos.	B	B				66.1	
Yaskin et al[9]	45	F	5 days	2D	2D	N	N	250	135	15
Drew & Magee[9]	38	M	7 wks.	3D	E	6/6	6/15	250	490	
Denny-Brown[10]	35	M	7 wks.	P	P			390	286	0
Krohn[11]	21	M	2 mos.	3D	3D	N	N		624	3
Dereux[12]	33	F		P	P	10/10	10/10	800*	1500	1
Feldman et al[13] (same case)	23	F	9 mos. 16 mos.	P 3D	P 4D	N	N	305	470 500	2 0

N—Normal H—"Hazy" R—"Reduced" C—"Choked"
M—"Moderate" B—"Blurred" E—"Elevated" P—Papilledema
*—Measured in sitting position

Decreased absorption, increased production, and a block in the cerebrospinal circulation pathway are basic mechanisms for production of hydrocephalus, according to Russel.[18] It is necessary to the theory of blocked absorption that hydrocephalus be demonstrated; however, Gardner and associates[14] failed to produce it in the experimental animal, and the ventricles showed "no shift or deformity" in the patient described by Denny-Brown.[10] In addition, the only other instances in which air studies were carried out are those of Ford and Walsh,[5] Dereux,[12] and the case reported here. In all cases there was no dilatation of the ventricular system. It was on the basis of normal sized ventricles on air study that Dandy[19] rejected the idea that a surfeit of cerebrospinal fluid could produce the increased intracranial pressure found in pseudotumor cerebri. He reasoned that there must be an increase in the volume of brain substance itself and stated, "If the fluid in the meninges were increased, the ventricular system would naturally participate and, therefore, be correspondingly enlarged from the backlog."

The mechanism producing increased intracranial pressure and papilledema in spinal cord tumors and small acoustic neurinomas is not analogous to the situation existing in the Guillain-Barré syndrome, since dilatation of the ventricles is produced in the former conditions but not in the latter. Love, Wagener, and Woltman,[15] in their report of spinal cord tumors with papilledema, felt that the increased protein was not a factor in producing the increased pressure and papilledema, but it could

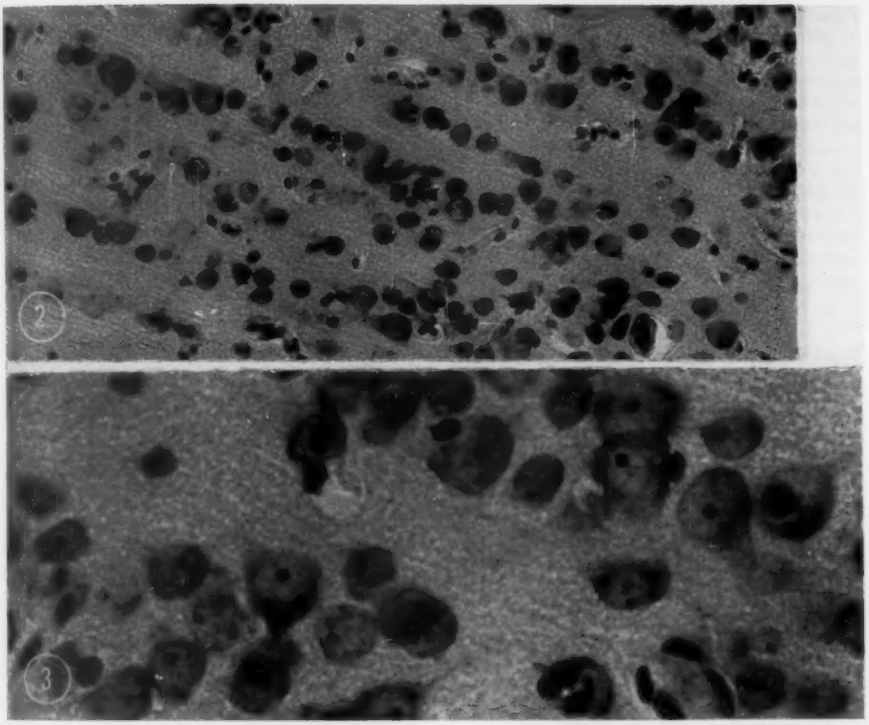

FIG. 2. Cortical biopsy, Nissl stain.

FIG. 3. Same section enlarged, Nissl stain.

result from a mechanical block anywhere along the neuraxis. The proponents of the high protein theory also cite the occurrence of papilledema in poliomyelitis with elevated cerebrospinal fluid protein as evidence to support their theory. It must be noted that in the one case report by Weiman, McDowell, and Plum[16] in which air studies were done, the ventricles were not dilated. Weiman and co-workers[16] concluded that the increased pressure and papilledema were due to cerebral edema secondary to the infection.

The conclusion drawn by Feldman and associates[13] that the alertness of the patient and the normal electroencephalogram preclude cerebral edema does not correspond with the well known findings in pseudotumor cerebri where cerebral edema has been verified pathologically.[20] In the large series of these cases reported by Foley,[21] Davidoff,[22] and by Sahs and Joynt,[20] mental alertness and a normal electroencephalogram were almost constant findings. The presence of a high Ayala index, which was cited to preclude cerebral edema, would depend upon the validity of the Ayala index and ascertaining the correct pressure values to place in the formula. In regard to the latter, Ecker[23] found pressure variations as great as 190 mm. of water (410-600) while measuring the cerebrospinal fluid pressure over a five-minute period in three cases of pseudotumor cerebri (cerebral edema). With such discrepancies in pressure determination, computation of the Ayala index would be difficult.

Finally, there is ample evidence in autopsy findings to support the contention that cerebral edema does occur in some cases of Guillain-Barré syndrome. This disease process affects not only nerve roots and peripheral nerves but the entire central nervous system. Roseman and Aring,[24] Polan and Baker,[3] Scheinker,[25] and Haymaker and Kernohan[26] all mentioned gross findings of cerebral edema or congestion in their examinations. Roseman and Aring[24]

reported that slight herniation of the uncus of the temporal lobe was present in all of their cases. These investigators reported various microscopic changes in the cerebrum as acute cell changes with swelling and chromatolysis, occasional shrinkage in the ganglion cells, congestion, petechial hemorrhages, swelling of the oligodendroglia in the white matter, and demyelination. The findings at operation of the present case as well as that of Ford and Walsh[5] exhibited swelling of the brain at the time of decompression. The biopsy in the present case demonstrated marked swelling of the nerve cells, with occasional chromatolysis. There was no evidence of inflammatory cells, vascular changes, or demyelination in any of the preparations from this biopsy. These findings resemble the gross and microscopic features encountered in cases of pseudomotor cerebri.[20]

In conclusion, it does not appear that increased cerebrospinal fluid pressure and papilledema found in the Guillain-Barré syndrome are a consequence of blockage of fluid absorption by high protein levels of the cerebrospinal fluid. It is more likely due to intrinsic cerebral edema similar to that found in cases of pseudotumor cerebri. It is possible that the factors responsible for the prominent nerve root edema in the Guillain-Barré syndrome may also result in cerebral edema in certain cases.

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The Grasping Deficit in Infantile Spastic Hemiparesis

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TREATMENT OR REHABILITATION of patients with disorders of voluntary movement resulting from central nervous system lesions depends, for its ultimate effectiveness, on a more complete understanding of the physiologic principles underlying the movement disorder. Although there is a great deal of literature concerning infantile spastic hemiplegia, the physiologic nature of the deficit has not been considered extensively. Though there may be involvement of face, arm, and leg on one side in infantile spastic hemiplegia, in the vast majority of cases the arm is most severely affected and particularly the hand, for there is a deficient ability to use the hand of the affected extremity with anything approximating the power and dexterity of the normal hand. The purpose of the present study is to point out some of the factors underlying this movement deficit in the upper extremity, particularly with regard to use of the hand for grasping an object.

It is important to realize that in infantile spastic hemiplegia, as well as in adult hemiplegia from whatever cause, there are wide variations in individual cases. Hemiplegia is not a static condition and, although all cases bear some general resemblance, close analysis of individual cases reveals clear differences. In a large series of cases, for example, there is considerable difference in the ability to use the affected hand. Some patients have a complete inability to move the upper extremity at all. Others may have the ability to flex or extend the arm at elbow or shoulder but an inability to use the hand. On the other hand, a few patients reveal only a very slight deficit in use of the hand, having perhaps a minimal clumsiness and weakness of the affected hand as compared with the normal, and again associated with only minimal neurologic signs. Between these extremes, however, there is a large number of patients who have some variable ability of use of the hand, though with obvious motor deficit, such as weakness, clumsiness, and slowness of movement. In this study we are not concerned with the wide variations of disorder of posture and movement seen in a large series of infantile spastic hemiplegia, but are rather more concerned with elucidating some of the factors contributing to the grasping deficit in that group of patients retaining some, although obviously deficient, use of the hand.

A series of 25 patients was observed at the Joseph P. Kennedy Jr. Memorial Hospital. These patients all fell into the latter group of infantile spastic hemiplegics, and several general principles appeared to operate in causing the deficient use of the hand for grasping. These patients have all been considered educable and rehabilitatable. They ranged in age from 11 months to 15 years. There were 13 left hemiplegics and 12 right hemiplegics. Fifteen of the patients were boys and ten were girls. There were 13 cases of congenital hemiplegia and 12 cases of hemiplegia acquired in the first few years of life. Of this group, five patients who were available for long-term inpatient study have been investigated intensively. Of these five patients, there were three girls and two boys.

Neurologic examination revealed obvious hemiparesis in these children, with far greater involvement of the upper extremity. The face was little involved, if at all. The hemiparetic extremities were rather smaller than normal. This smallness again was more pronounced in the upper extremity than in the lower. Hemiplegia in all of these cases was spastic in nature and revealed slight to marked exaggeration of deep tendon reflexes on the affected side and an extensor plantar response. Being particularly concerned with the status of the upper extremity, we noted that spasticity was very slight or absent in the shoulder muscles and, when present, appeared in the retractors and adductors. There was mild to moderate spasticity in the elbow flexors and mild to moderate spasticity in the wrist and finger flexors. The resting posture of the upper extremity was only slightly affected, there being a slight flexion of the elbow and retraction of the shoulder. The resting posture of the wrist was of slight flexion. The change in the rest-

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ing posture of the affected upper extremity was most noticeable in the hand and was quite similar in all cases with a few variations. In all patients the fingers of the affected hand were flexed slightly more than those of the normal hand. However, in none of the patients was this flexion so marked as one sees in the severely spastic and paretic hand. Anomalies of posture were more prominent in the thumb, the thumb being generally adducted more than normal and the distal phalanx of the thumb being extended more. In one patient there was a slight extension of the proximal interphalangeal joints of the fingers, but again approaching in no way the subluxation seen in certain severely spastic hands. Examination of sensation revealed no deficit whatsoever in appreciation of pin-prick in any of the patients. Position sense in the affected fingers was poor in two patients, but without clearly demonstrable extinction phenomena or disorder of tactile perception. The other patients revealed no abnormality of sensation and, indeed, the presence or absence of a sensory deficit did not affect any of the physiologic mechanisms to be described. A grasp reflex of the deep, pressing contact type, as described by Seyffarth and Denny-Brown,[1] could not be obtained in any of the affected hands. Little if any diminution in power of willed movement was demonstrated in the shoulder or elbow muscles. However, strength of both flexion and extension was obviously impaired in the wrist and fingers, extensor movements being more impaired than flexor. These deficits will be detailed in another section of this paper.

DESCRIPTION OF THE GRASPING DEFICIT

From the onset a slowness of the act of grasping in the affected extremity was apparent. If the patient was given the command to grasp, there was a latent period from the time of command to the time of onset of reaching out to grasp, which was one to three seconds longer than that of the normal limb. This latent period could be detected even though the patient was not required to reach out, the object being kept in close proximity to the hand. Again, from the beginning of the grasping act, the slowness of movement was striking, not only in reaching out to grasp, but in actual flexing of the fingers around an object. This slowness of movement might not be explained entirely by the presence of spasticity. Once the latent period had been overcome and the movement to reach out to grasp had commenced, a rather striking ataxia was noted which again was variable in different patients, the variability being more of quantity than of quality. This ataxia was manifest as an overextension* of fingers and occasionally of wrist as the hand reached out to grasp (figure 1). The extension of the fingers might be slight or it might be most pronounced, and could also be associated with slight or wide abduction of the fingers. The extension of the fingers primarily was of the metacarpophalangeal joints, but there might also be strong extension of the interphalangeal joints. The thumb, which in the resting posture had been primarily in an adducted position, did not participate so markedly in this overextension phenomenon. On reaching out, the thumb could abduct slightly, but generally remained in an adducted position with slight to strong extension of the distal phalanx. In several patients, however, there was strong extension and abduction of the thumb as the patient extended the affected limb to grasp. This variable overextension of the fingers and occasionally of the wrist in the hemiparetic extremity was in marked contrast to that of the normal hand. As a normal hand reaches out to grasp an object, the fingers remain in a semi-flexed position, particularly at the interphalangeal joints, with only a slight extension and abduction. Associated with the overextension seen in the hemiparetic limb was a certain wavering ataxia of the limb which could not be related to weakness alone, since proximal muscle weakness could not be demonstrated.

Further deficits were apparent once the object had been grasped. First of all, there was an obvious weakness of grasp, several aspects of which will be discussed later. This weakness appeared to have a rather peculiar quality in that it was not manifest as a gradual diminution of strength of grip. Rather, one was impressed by a fluctuating or undulating change in the power of the grip. There was an inability to sustain even a weak grasp over a long period of time, and in such an attempt this fluctuating quality of diminishing strength was striking. Certain manifestations of the weakness of the grip were seen in day-to-day activities of the children, during which they would drop from the affected hand very light objects which should have been easily carried in the hand.

Analysis of the posture of grasping revealed nothing striking in the hand itself, except that again the thumb often remained too adducted

*Extension of fingers or wrist implies dorsiflexion of these parts.

and the distal phalanx of the thumb remained extended rather than flexing around the object. The most striking feature of actual grasping, however, was seen in the reaction of the synergistic and fixating muscles during the process of grasping. When an object is grasped with a normal hand, as the fingers flex around the object, the wrist extensors act synergistically with the flexors of the fingers in order to fixate the wrist so as to enable an efficient grasp and one of maximal power. In a powerful normal grasp there is fixation of the elbow by contraction of the biceps and triceps muscles. In infantile spastic hemiparesis a breakdown of this normal grasping mechanism was a striking feature. There was lack of fixation of the wrist and apparently no synergistic action of the wrist extensors. Instead there occurred a strong flexion of the wrist as the fingers flexed to grasp an object, that is, there was synergistic flexion of the wrist occurring simultaneously with the flexion of the fingers. It was further apparent that in infantile spastic hemiparesis there was not the normal fixation at the elbow joint, but rather again a simultaneous flexion of the elbow occurring with the flexion of the wrist and fingers and also a slight flexion or retraction of the shoulder, particularly with effortful grasp (figure 2). It was clear then that the flexion of the fingers to grasp an object occurred as part of a flexor synergy of the upper extremity. It must be emphasized, however, that there were variations in this response in different patients. Many patients revealed the entire flexor synergy as they grasped an object with moderate power and revealed the synergy most strikingly if they produced a strong effort of grasping. However, if these same patients grasped with only slight power, the complete flexor synergy might not be evident, but only the slight flexion of the wrist. Careful palpation revealed that there was a slight contraction of the biceps, but none of the triceps. Other patients revealed the response only in fragmentary form, as a slight flexion of the wrist accompanying the flexion of the fingers even under conditions of strong effort of grasping. In other patients and particularly those who had been trained to consciously extend the wrist at the time of grasping, one had the impression that the flexor synergy was not operative and that normal fixation of wrist occurred. However, if these patients were fatigued by repeated grasping, the flexion of the wrist occurred most strikingly and was occasionally associated with the entire flexor synergy of the upper extremity. Some evidence for the flexor synergy was found in every patient who retained some ability of grasping in the hemiparetic extremity.

The failure of wrist fixation in the spastic extremity and the strong synergistic flexion of the wrist which accompanied flexion of the fingers as they grasped an object immediately suggested one mechanism for weakness of grasping in the affected hand. Dynamometer studies of the grip in the affected extremities of these patients revealed diminution in strength to 20 to 30 per cent of normal when the patient was allowed to grip the dynamometer in his usual manner. However, if the wrist was fixated artificially by splinting, the strength of grasp increased to 40 to 60 per cent of normal. Thus, some loss of strength was obviously related to the mechanical disadvantage offered to the finger flexors by the synergistic flexion of the wrist and consequent loss of fixation of the wrist. A major part of the weakness then could be attributed directly to the breakdown of the normal mechanism for fixation of the wrist.

It was clear that several features occurred most strikingly in the deficient grasping in infantile spastic hemiparesis aside from the slowness, clumsiness, and lack of dexterity in the affected hand. These features appeared to be primarily an ataxia manifested as an overextension of fingers and occasionally of wrist as the hand reached out to grasp an object, and secondly, a dissolution of the normal fixation of wrist and elbow as an object was grasped. This fixation of wrist and elbow was replaced by flexion at these joints so that the ability of grasping in the affected limb was seen as part of a flexor synergy of the upper extremity.

NATURE OF THE FLEXOR SYNERGY

The lack of fixation of the wrist and elbow in the hemiparetic extremity and the replacement of this normal mechanism by a flexion of the wrist and occasionally of elbow and shoulder appearing synergistically with the flexion of the fingers suggested some general principle operating in all these cases. This flexor synergy was identical to that which we described in 1951[2] as a stage in recovery of motor function in adult hemiplegia. At that time we pointed out that the earliest return of finger flexion in the adult recovering from hemiplegia occurred as a part of a flexor synergy of the upper extremity, and we related the flexor synergy to an elaboration of a reflex response, the traction response. The traction response consists of a flexion of wrist, elbow, and shoulder and slight

flexion of the fingers elicited reflexly by a strong passive abduction of the shoulder in order to stretch the adductor muscles of the shoulder. A striking feature of this response is the strong flexion of the wrist.

The development of the traction response and its eventual elaboration into voluntary grasping in infantile spastic hemiparesis is illustrated in the following case:

The patient was an 11 month old male infant who had developed normally prior to his present illness. He had begun to walk and talk and had already shown a marked preference for using the right hand, particularly for prehensile activity. He was seen in neurologic consultation on November 19, 1954 because of continuing convulsions. Prior to the onset of convulsions the child had had a high fever and had been dehydrated for several days. When the child was first seen, the seizures had ceased and he evidenced a right flaccid hemiplegia, with head and eyes deviated to the left. Reflexes on the right were increased and the right plantar response was extensor. A diagnosis of sagittal sinus thrombosis and thrombosis of the left cortical veins was made. On December 28, 1954 the child was seen again. He was unable to stand or talk and he had a right spastic hemiplegia. At the time of this examination occasional flexions or extensions of the right arm and leg occurred if the child moved his head, either actively or as the examiner moved it passively, and it was clear that the movements of these limbs were related to the tonic neck reflex. It was also noted that a passive stretch of the adductors of the right shoulder caused a weak synergistic flexion of the wrist, elbow, and shoulder. There was at this time only a very slight, weak flexion of the fingers associated with this response. One month later the child was beginning to stand, but still did not use the right hand. However, a passive stretch of the right shoulder adductors caused a very facile synergistic strong flexion of the entire limb, in which response the flexion of the wrist to 90° was most prominent. Flexion of the fingers associated with this response was more powerful at this time. At another month interval the child was able to walk. He did not use the right hand spontaneously for grasping, but he could be persuaded to reach out with the right hand if the left one was restrained. He would fling the hand at an object and, if the fingers hooked over the object, they would flex around it. The child might be induced to carry an object, such as a lollipop, to his mouth. Flexion of the fingers for grasping occurred as part of a total flexor synergy of the upper extremity. Since the time of this examination there has been continuing improvement in the use of the right hand; however, there is still evidence of retention of the flexor synergy, and the synergistic movement itself can be facilitated by stretch of the shoulder adductors.

In this patient it was concluded that the voluntary ability to grasp which returned was related to a learned adaptation of a reflex response, the traction response. Further analysis of our other patients revealed that their ability to grasp was an elaboration of this response.

In most instances passive abduction of the affected shoulder so as to stretch the shoulder adductors caused little change in actual position of the elbow, wrist, and fingers of the affected extremity. That this maneuver did have some effect on the postural activity of the muscles of the affected extremity was apparent, however, and was easily demonstrated by comparing resistance to passive movement in the elbow, wrist, and finger flexors with the arm abducted at the shoulder and in the adducted position at the side of the body. With the shoulder abducted so as to stretch the adductors there was a marked increase in resistance in the elbow, wrist, and finger flexors of the affected extremity. When the extremity was then placed in the adducted position, the resistance diminished markedly. A passive stretch of the shoulder adductors could also increase the power of grip. Thus, if, as the patient grasped the examiner's hand, the examiner gave a strong pull on the hand so as to stretch the shoulder adductors, the power of grip was increased.

Change in spasticity or in the power of grip could also be influenced by position of the head in relation to the body, or position of the body in relation to a bed or broad surface. Thus, in a right hemiparetic, for example, the strength of the grip in the right hand was increased and spasticity of the hand was increased as the patient turned his head so as to turn the face to the left. Strength of grip and spasticity decreased as the face turned to the right. In like manner if this patient were placed on the bed on his left side so that the right hemiparetic limb would be uppermost, strength of grip in this limb and spasticity were increased. If he lay on his right side so that the right hemiparetic limb was lowermost, strength of grip and spasticity decreased.

Further evidence for synergistic reaction was clear when the patient was instructed to voluntarily flex another segment of the limb, particularly against resistance. If the patient was instructed to flex the elbow, it was noticed that the entire extremity flexed, that is, there occurred simultaneously flexion of the shoulder, wrist, and fingers along with the elbow. He could not produce flexion of the elbow as an isolated movement. Again, if the patient was instructed to flex only the wrist, he was unable to do this in an isolated fashion and such an

FIG. 1. Overextension and abduction of fingers as hand approaches object.
FIG. 2. Two phases of flexor synergy. In lower photograph, effort of grasp has been increased.
FIG. 3. Two phases of reaction of hand to contact stimulation of palm.

attempt caused associated flexion of fingers, elbow, and shoulder. It was clear that flexion synergy of the extremity was not related only to flexion of the fingers in a willed manner. These phenomena were variable. In some patients, although an apparent isolated flexion of one joint of the extremity could be obtained without initiating the flexor synergy, the predominant synergistic activity was evidenced if one carefully palpated the other muscles of the extremity, in which instance one could feel simultaneous contraction of the other flexor muscles.

In some children the traction response was not well enough developed to enable useful grasping with the hand. For example, one child with left hemiplegia did not use the hand voluntarily to grasp, but, with persuasion, he could fling the hand at an object and hook the fingers around it rather poorly, at which time the fingers would flex slightly and weakly only if the patient were instructed to flex the

elbow and shoulder. It was noted that the wrist, elbow, and shoulder flexed synergistically and that the fingers also joined in this synergy, but with too little power to enable a useful grasp.

Children who did not reveal any evidence of the total flexor synergy or in whom a traction response could not be elicited in any form were also unable to use the affected upper limb for effective grasping. Some children did reveal some flexion and extension movements at proximal joints (probably as an adaptation of the tonic neck reflex), but without any movement of wrist and fingers. Use of the hand for grasping never occurred in this group.

NATURE OF THE OVEREXTENSION PHENOMENON

As described earlier, all patients revealed some overextension of fingers and occasionally of wrist as the hand approached the object. In some cases the extension was more pronounced than in others and occasionally could be associated with marked abduction of fingers and thumb and extension of wrist. This posture was also present in the affected limb when the patient held both arms outstretched before him. Under such conditions a slight eversion of the hand in addition to the overextension was apparent. It was clear, however, that some evidence of this response was present in all patients, and we were interested in establishing the nature of this response.

That this extension was primarily related to an active extensor synergy of the extremity occurring as the arm extended to reach for an object was ruled out. First of all, the overextension occurred whether the arm extended actively to grasp or not, for with the patient's arm held close to the side and the object to be grasped in close proximity to the hand so that there would be no need for extensor movement of the arm to grasp the object, the extension of the fingers still occurred as the object approached the hand and a careful palpation of the muscles of the extremity revealed no evidence of activity in the proximal extensors. Secondly, if the patient merely extended the arm in front of him, the extensor response of the fingers did not occur.

The identical response could be initiated without the patient's voluntary effort by certain contactual stimulation of the hand. For example, strong distally moving contact stimulation of the palm produced the identical response, that being extension of the fingers with or without abduction and with or without extension of wrist (figure 3). In some patients slight abduction of thumb also occurred with this type of stimulus. Stimulation was more effective if delivered to the ulnar side of the hand, and in some patients the reflexive zone was limited to the ulnar side. However, in some patients the response could be elicited by similar stimulus to any part of the palm. In general, stimulation of the ulnar side caused slight eversion of the hand and stimulation of the radial side caused slight inversion. It was also noticed that, during the process of spontaneous grasping and release of an object, some overextension of the fingers occurred at the time of release of the object if the object happened to stroke the skin of the palm as it was released. Extension of the fingers as the hand reached out to grasp and the extension produced by this contactual stimulus to the hand did not appear to be related to any sensory disorder. It occurred in all patients, regardless of the presence or absence of sensation described earlier, particularly position sense deficit and extinction phenomenon. Indeed, response was most striking in a child who revealed no evidence of sensory disorder whatever.

It was interesting to note in these patients that, although voluntary extension of the wrist and fingers as a willed performance was extremely weak and of short duration, the power of extension of fingers and occasionally of wrist as the hand reached out to grasp an object, or as produced reflexly by contactual stimulation, was far greater than that produced by voluntary effort of extension.

It was also found that strength of grip or finger flexion could be influenced by simultaneous contactual stimulation of the palm, as described above. Thus, it was found on dynamometer studies that the strength of finger flexion could be diminished 40 to 50 per cent by concomitant contactual stimulation of the palm as the patient evoked a willed flexion of the fingers. This phenomenon suggested another mechanism for weakness of grasp in these patients and particularly the fluctuating diminution in strength of grasp. It is clear that the object grasped can itself provide contactual stimulation to the skin of the palm which may, in turn, produce a movement of the fingers completely antagonistic to the movement required for grasping.

DISCUSSION

In infantile spastic hemiparesis the deficit in voluntary grasping is apparent from the very

onset of the voluntary effort in the slowness of the motor response and the latent period in initiating it. Further deficiencies then appear as the action continues, for an obvious lack of dexterity and clumsiness occurs as the hand approaches the object to be grasped. The fingers overextend and often abduct widely; this movement may be associated with extension of the wrist. As the digits close around the object the wrist flexes, often acutely, and if the power of grip is increased, an associated flexion of elbow and shoulder may occur. There is an obvious weakness of the grasp which has a fluctuating quality.

A detailed analysis of the action of the muscles utilized for grasping was made by Beevor.[3] He pointed out that, in grasping, all the flexor muscles of the fingers and thumb contract and the wrist extensors contract simultaneously to fix the wrist. Beevor quoted an illuminating remark of Duchenne who stated, "that the synergic action of the extensors of the wrist is absolutely necessary to the flexion of the fingers, and the force of their contraction is then proportional to the energy of this flexion."

Beevor further pointed out that, although for a weak grasp only the finger flexors and wrist extensors need contract, if a more powerful effort were made, other muscles also contracted, these being the flexors and extensors of the elbow and perhaps the shoulder muscles. He also noted in such instances during a powerful grasp that, although both biceps and triceps contracted, the triceps contracted first.

From his detailed studies of muscular action Beevor suggested a classification of muscles participating in any movement as: 1) prime movers, 2) synergic muscles, and 3) fixation muscles. For the act of grasping, therefore, the prime movers are the flexors of the fingers and thumb, the synergists the wrist extensors, and the fixators the biceps and triceps.

A breakdown of this normal mechanism contributes significantly to the grasping deficit in infantile spastic hemiparesis. Disturbed function is evident not only in the prime movers but also in the synergists and fixators. There is an obvious weakness and clumsiness affecting the prime movers, which we shall comment on later. More striking at this point, however, is the absence of normal contraction of the synergists (wrist extensors) and the fixators (elbow flexors and extensors), and a replacement of these responses by those of flexion of the wrist and of the elbow as part of a total flexor synergy of the hemiparetic limb.

A similar upset of the normal activity of synergists and fixators in the hemiparetic limb has been commented on by others.[4,5] Foerster[6] discussed the synergistic flexion of the arm and the inability to isolate the various individual contributing movements after excision of the rolandic motor cortex in man.

In 1951 we reported a study[2] concerning the return of motor function after hemiplegia in the adult and pointed out that the course of recovery took the form of a series of reflex changes, each accompanied by increasing ability of willed movement. Simple segmental proprioceptive reflexes returned first and were eventually modified by stretch of the muscles concerned, tonic neck and body righting reflexes. The first ability of willed finger flexion occurred as part of a total flexor synergy of the upper limb, the individual components of which could not be isolated by the patient at that particular stage in the recovery process. Prior to recovery of this ability for willed finger flexion, flexion of the fingers as a part of a flexor synergy of the arm could be induced reflexly by strong traction on the limb so as to stretch the shoulder muscles. Such a maneuver then elicited (by virtue of increasing spasticity) simultaneous contraction of the shoulder, elbow, wrist, and fingers. When the first weak ability of willed finger flexion had recovered, it could be facilitated by this shoulder stretching procedure and related proprioceptive mechanisms and could be facilitated or depressed by appropriate methods for eliciting the tonic neck or body righting reflex patterns. It was clear that the first ability of willed finger flexion was an adaptation of this reflex synergy.

This reflexive response took the same form as one observed in the monkey with rolandic motor cortex or pyramid lesion and was named the "traction response." Denny-Brown, Twitchell, and Saenz-Arroyo[7] identified this response with the grasping of the thalamic animal, and Bieber and Fulton[8] demonstrated this response as a body righting reflex. The traction response, as shown previously, is distinct from the true grasp reflex,[1,7] is initiated by passive stretch of the shoulder muscles, and can be obtained after cutaneous denervation of the limb.[9] The monkey with area 4 or pyramid lesion soon learns to utilize this response for spontaneous grasping, projecting the arm and hooking the fingers around the object.

The usual action of the wrist extensors as synergists and biceps and triceps as fixators is disrupted by virtue of operation of this flexor

synergy. A striking feature of the response when fully developed is an acute wrist flexion. The substitution of flexion of the wrist for the normal fixation or slight extension certainly causes mechanical disadvantage and consequent weakness of grasp.

It is clear that the ability for willed grasping in the patients with infantile spastic hemiparesis is an adaptation of the traction response. Its evolution into willed movement has been traced in the case cited, and in the other patients the flexor synergy took an identical form and could itself be modified in like manner by appropriate stretch or by neck and body reflexes. Thus, it is clear that the ability for willed movement in these patients is related to utilization of a subcortical mechanism and not the vicarious function of some other region in the cortex of the same or opposite hemisphere.

The overextension of the fingers and occasionally the wrist as the hemiparetic hand approached to grasp an object and the occasional overextension of fingers as the hands were held outstretched before the patient bear a marked similarity to a posture exhibited by patients with parietal lobe lesions, as pointed out by Denny-Brown and his co-workers.[10–12]

In patients with parietal lobe lesions the arm opposite the side of the lesion may reveal curious abnormalities of posture. When the arms are outstretched the hand of this limb may evert and the fingers extend, and this movement may be facilitated by tactile stimulation of the hand or by the presence of another individual in the corresponding visual field such as to cause the whole limb to rise (levitation phenomenon). As the patient reaches out to grasp an object, the fingers overextend in a manner similar to that reported here.

Denny-Brown[11,13] has related the levitation phenomenon to the instinctive avoiding reactions occurring in the limb opposite parietal lobe lesion in the monkey. The avoiding reactions can be elicited either by visual or tactile stimuli and consist of a flexion of the limb away from the stimulus.

We have been particularly interested in the description by Denny-Brown and Chambers[12] of the tactile avoiding reaction occurring in response to contactual stimulation of the palms. When facile this consists of an initial extension of the fingers, followed by a flexion of the fingers and supination of the wrist. This reaction is then followed by a flexion of the limb at all joints so as to fold the hand away from the stimulus. A more delicate form of response consists of an extension of the fingers and wrist with inversion or eversion, depending on the side of the palm stimulated.

Although the avoiding reaction has been most prominent after parietal cortex lesions in the monkey, it can also be demonstrated following area 4 ablation in the monkey, taking the form of slight extension of the fingers.

We would identify the initial overextension of the fingers in the patient with infantile spastic hemiparesis with the avoiding reaction. The response in our patients assumed an identical form and could be initiated or facilitated by contactual stimulation of the palm. We could not demonstrate any visual facilitation.

Denny-Brown[13] has pointed out the overemphasis on the flexor phase of movement induced by the avoiding response and proposed this as a major factor in parietal lobe apraxia, pointing out that deficit in position sense does not always occur. We have also found this response to be facile in our patients, even when a sensory deficit could not be demonstrated, and it appears that this reaction may also be significant for the ataxia of the hemiparetic limb which itself is most prominent in movements of extension. We have previously commented on the probable role of the avoiding response in contributing to weakness of grasp. We would further suggest overactivity of this response as contributing to the latency preceding the onset of grasping.

In our previous study documenting the events in recovery from hemiplegia,[2] it was pointed out that, if recovery of willed movement proceeded beyond the flexor synergy, then the predominate proprioceptive responses changed due to conditioning by contactual mechanisms. Thus, if the grasp reflex (a subcortical response) returned, spasticity not only diminished but power and dexterity of willed movement increased. Isolated movements of the digits and finger-thumb opposition, previously impossible as a willed response, were restored.

Full recovery could not occur unless the mechanism for the elaborate cortical response, the instinctive grasp reaction, was intact. Nevertheless, the degree of recovery associated with return of the grasp reflex was so remarkable that the failure of this response in infantile spastic hemiparesis assumes considerable importance.

Further understanding of these problems has recently been provided by Denny-Brown[13] who has demonstrated that the cortical in-

stinctive grasping reactions and instinctive avoiding reactions are in equilibrium and that a lesion abolishing one allows the other to become overactive (transcortical release). Thus, a frontal lesion may abolish avoiding and release grasping, while a parietal lesion causes the opposite effect.

Such an analysis provides further understanding of the deficit following lesion of the rolandic motor cortex. Ablation of this cortex abolishes the instinctive grasp reaction and allows subcortical release in the form of spasticity (traction response). Transcortical release is seen as overactivity of the avoiding response. Curiously, the subcortical grasp reflex is also impossible or extremely difficult to obtain following a rolandic lesion, although it is clear that the mechanism is intact for, with strong stimulus, it may be obtained. Denny-Brown regards the overactivity of the avoiding response as responsible for the failure of the grasp reflex and explains the paradoxical improvement in infantile spastic hemiplegia following hemispherectomy as the result of abolition of the avoiding mechanism and consequent recovery of the grasp reflex.

In man these changes are better demonstrated in hemiparetic children than in adults. Subcortical release is evident in both as spasticity (often elaborated into the traction response). Transcortical release as the avoiding reaction is more easily demonstrated in children, although its features may be seen in fragmentary form in the adult.

CONCLUSION

The ability for voluntary grasping in infantile spastic hemiparesis results from a learned adaptation of the traction response as a flexor synergy of the upper limb. The synergistic flexion of wrist and elbow, however, contributes to deficient power of grasping, owing to the mechanical disadvantage interposed by such flexion.

There also occurs a slowness and loss of dexterity related to overactivity of the avoiding response, manifest as an initial extension of fingers and wrist as the hand approaches to grasp an object. This factor may also induce further weakness as the object grasped provides contactual stimulus for an antagonistic response.

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Effects of Brainstem Lesions on Optokinetic Nystagmus in Monkeys

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OPTOKINETIC NYSTAGMUS is a phenomenon which is brought about through a visual stimulus and oculomotor effect. The nervous system substrate for this phenomenon must be the optic nerve for the input and the oculomotor nerves for the output. However, the internuncial connections between the input and output are not well known. Spiegel,[1] who reviewed the subject of optokinetic nystagmus in detail, refers to his own work and to that of others and concludes that "optokinetic nystagmus is a reflex actuated by way of the cerebral cortex . . . . the afferent limb is constituted by the corticopetal optic pathway, the efferent limb by the . . . . cortico-fugal fibers proceeding from the optomotor zone of the occipital lobe." Stenvers[2] postulated that the optokinetic response is a cerebral reflex subserved partly by a path between the calcarine region and the frontal lobe. The clinical observations of Fox and Holmes[3] tend to support Stenvers' hypothesis that "reflex centers" for optokinetic nystagmus lie in the occipital lobe and the second frontal convolution and that these are connected by a "reflex path" which runs through the white matter of the hemisphere. Others have indicated that optokinetic nystagmus is essentially a brainstem reflex. Dix, Hallpike, and Harrison[4] emphasized the independence of the optokinetic nystagmus of the vestibular nuclei. Spiegel,[1] who had a broader concept, stated that the brainstem participated in optokinetic nystagmus and that impulses coming from the occipital lobe projected into the median longitudinal fasciculus. Strauss[5] discussed the element of "visual attention" in production and abolition of nystagmus. In recent papers Carmichael, Dix, and Hallpike[6] and Enoksson[7] considered the effect of cerebral lesions on optokinetic nystagmus. Rademaker[8] brought forth the hypothesis of a "feedback" mechanism. From these varying opinions, it is obvious that the anatomic and physiologic basis for this phenomenon is still not clear. The purpose of this communication is to present data which may give us more information on the pathways in the brainstem which mediate the impulses involved in optokinetic nystagmus. The method employed was to make electrolytic lesions in the brainstem and note the effect on the opticomotor response in monkeys.

METHOD AND MATERIAL

Fifty-seven adult monkeys (Macaca Mulatta) were used in this study. Before the electrocoagulation lesion was made each animal was examined neurologically for eye movements. Special examinations were performed, such as Barany rotation tests, cold water stimulation of ear canal, and optokinetic stimulation induced by a rotating striped drum.

Operations were performed with the aid of stereotaxic instruments under Nembutal anesthesia, 30 mg. per kg. of body weight. Using sterile technic, a trephine opening was made over the midline vertex between the ears. A bipolar electrode was lowered into the brainstem through a Horsley-Clarke stereotaxic instrument. Electrolytic lesions were made in specific regions of the brainstem determined by previous electrostimulation studies. The coagulation was made through a DC coagulator, using a current of 4 ma. for one minute.

Postoperatively the animals were examined repeatedly and tested as mentioned above. The oculomotor responses (nystagmus) were recorded through an eight-channel electroencephalograph with three gramophone needle electrodes inserted in the skin, one in each anterior temporal region just lateral to the external canthus and one over the bridge of the nose between the eyes.[9,10]

To evoke the optokinetic nystagmus, the monkey was placed within the center of a large rotating cylinder 24 inches in height and 36 inches in diameter. This cylinder was constructed of Moldrite, a white, translucent plastic with a matted surface. At intervals of 13¾ inches along the inside surface of the cylinder there were black stripes one inch in width and as high as the drum itself. In all, there were eight black stripes which appeared as the figure against a white background. The top of

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the cylinder was closed by a darkly stained piece of wood which had a source of illumination at its exact center, thereby lighting the inner surface of the cylinder evenly at any given level. An outside rim drive allowed the entire apparatus to be rotated about its vertical axis. The speed of rotation was kept constant by a servo-controlled motor which could turn the cylinder in either direction at any speed up to 60 revolutions per minute. The direction of rotation in front of the monkey will be indicated by R-L for right to left and L-R for left to right.

The monkey was placed in a restraining box in a seated position, with the head straight forward and slightly dorsiflexed. This box was put inside the cylinder along the center of rotation in such a way that the monkey's field of vision was entirely filled by the inner surface of the drum. The source of light was directly overhead and therefore was invisible and did not project a shadow into the field of vision. The optokinetic nystagmus was indirectly observed with the electroencephalograph by recording changes in the resting corneo-retinal potential produced by movement of the

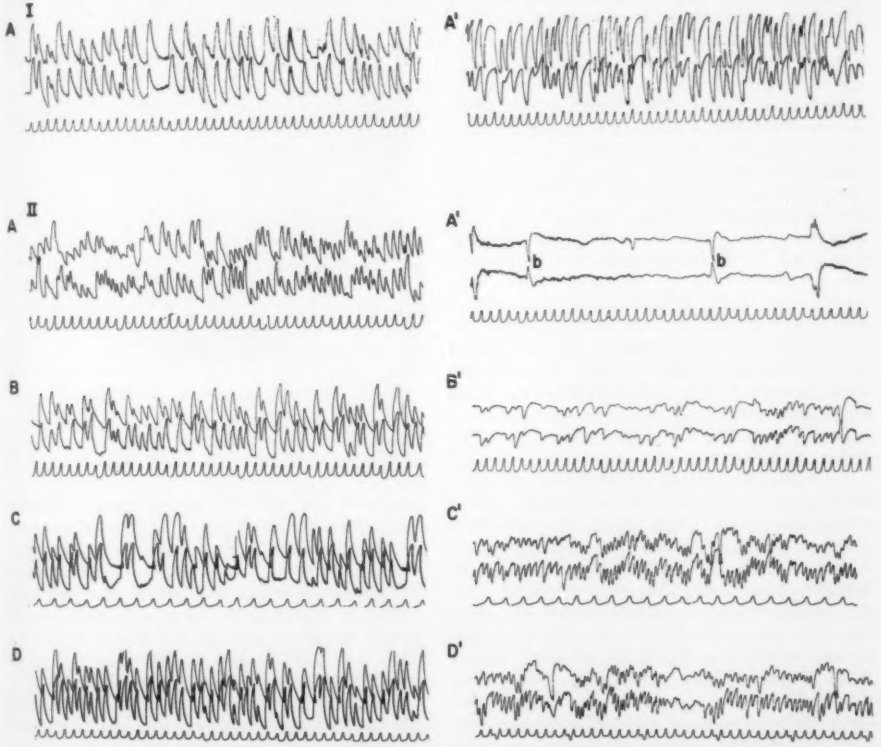

FIG. 1. Changes in optokinetic nystagmus in monkey 35 before and after a lesion was made in the left paramedian zone reticular formation of the pons.

I. Preoperative optokinetic nystagmus illustrated electrooculographically. Test made on October 7, 1954. Control study. Sharp upward rise indicates jerk to the right, while sharp downward deflection indicates jerk to the left. Drum rotated at 14 r.p.m. or 112 stripes per minute. *A*. Right to left rotation. *A'*. Left to right rotation.

II. Postoperative optokinetic test made on October 20, 1954 or 13 days after an electrolytic lesion was made. The speed of drum rotation was as before. *A*. Right to left drum rotation—normal response. *A'*. Left to right drum rotation—no optokinetic response. Test made on twenty-third postoperative day: *B*. Right to left drum rotation—normal response. *B'*. Left to right drum rotation—revealed an irregular and defective optokinetic nystagmus. Test on fifty-first postoperative day: *C*. Right to left drum rotation. *C'*. Left to right drum rotation disclosed a rapid and fine optokinetic nystagmus. Similar result was obtained with slower speed of rotation. Test on eighty-sixth postoperaive day: *D*. Right to left rotation. *D'*. As in *C'*.

eyeballs. To correlate the rate of drum rotation with the optokinetic nystagmus thus induced, a photoelectric cell was fixed outside the drum. The moving black stripes deactivated the cell and marked the rate of drum rotation.

Anatomic studies were made at scheduled intervals. The animals were sacrificed under general anesthesia. The brain, including the brainstem, was removed and fixed in 20 per cent formalin. A block of tissue, which included the whole brainstem, was cut serially after it had been embedded in paraffin or celloidin. Each section was 25 microns in thickness and each tenth to eleventh section was stained by the Weil method.

RESULTS

In each of the 57 animals used in this study, the preoperative optokinetic test showed a normal and symmetrical response in either direction of drum rotation. The quick and slow components can be readily identified in the electrooculogram (figure 1). In the R-L rotation the quick component was to the right and illustrated in the electrooculogram by a sharp rise in the curve. In the L-R rotation the eyes jerked to the left, illustrated by a sharp downward deflection. In none of these 57 animals was the optokinetic nystagmus absent or defective in the preoperative test. The responses were regular and rhythmic and could be obtained at speeds from 7 to 14 r.p.m.

In the postoperative state there were two types of defects:

1. *Complete loss or impairment of optokinetic nystagmus on ipsilateral rotation.* There were 24 monkeys in this group. In all of these animals anatomic studies revealed the lesion to be primarily in the paramedian zone of the reticular formation. This zone extended from the caudal end of the midbrain into the pons and was situated ventral to the median longitudinal fasciculus, dorsal to the dorsal fibers of the trapezoid body, and within 3 mm. from the median raphe. In some animals the lesion destroyed not only the reticular formation but also part of other adjacent structures. In some the tectospinal tract was injured. In others the adjacent medial longitudinal fasciculus was partly damaged; the structure damaged depended upon the location of the lesion in the dorsoventral dimension of the brainstem. The size of the lesions varied from 1½ mm. in diameter to 4 by 2 by 3.5 mm. (figure 2). The major lesion, however, was in the reticular formation. In fact, it was this lesion which

FIG. 2. Myelin sheath stain of section of brainstem cut in the plane of the stereotaxic instrument. The needle track is seen to pass through the central gray matter. The electrolytic lesion is in the left paramedian zone situated above the fibers of the abducens nerve.

produced the greatest disturbance in oculomotor function, manifested by paralysis of ipsilateral conjugate gaze and defects in the optokinetic response. Following an electrocoagulative lesion made in the paramedian reticular formation of the pons, there was paralysis of ipsilateral gaze.[11] If any movement returned, there was either a loss or defect in the optokinetic response. Twelve animals lost the optokinetic response in one direction, one in both directions of drum rotation, and in 11 monkeys optokinetic nystagmus was present but defective on the side of the lesion. By defective response we mean that the optokinetic nystagmus was irregular and arrhythmic as recorded on the electrooculogram. The absence of optokinetic response was always in the direction of rotation from the side of the lesion in the brainstem. That is, if the lesion was on the left side of the pons, the L-R rotation would result in either defective or no optokinetic nys-

tagmus. Rotation of the drum from the side opposite to the pontine lesion resulted in normal optokinetic response in every instance.

In eight monkeys loss of optokinetic nystagmus was considered permanent throughout the survival period from 33 to 480 days. One animal, in whom the lesion extended across the midline and involved both sides of the paramedian zone of the brainstem, showed a loss of optokinetic response in both directions of drum rotation. This monkey died on the fourth postoperative day. Another animal who showed a loss of optokinetic nystagmus in one direction died on the third postoperative day. In five monkeys the loss of optokinetic nystagmus was transitory, lasted two to 45 days, and thereafter became permanently defective. Two other monkeys showed no loss of optokinetic response but had a defective response in one direction of rotation for a survival period of 13 and 28 days, respectively.

The abnormal optokinetic responses were associated with paralysis or paresis of ipsilateral conjugate horizontal gaze in 15 monkeys. In each of these animals there was a defect of gaze to the side of the pontine lesion and the eyes were persistently deviated to the opposite side. Eight monkeys had a permanent paresis of ipsilateral gaze, with a complete loss of optokinetic nystagmus. In seven monkeys the paresis of conjugate lateral gaze was transitory. With this there was an associated loss of optokinetic nystagmus. As the paresis of conjugate gaze lessened, the optokinetic nystagmus reappeared but remained persistently defective throughout the survival period of each animal.

In nine monkeys with a lesion in the left side of the brainstem 1 to 3 mm. lateral to the midline, there was no paralysis of ocular deviation. Nevertheless, the optokinetic response was found to be defective in eight monkeys. This defect was apparent during L-R rotation. In another monkey the optokinetic response was abnormally fast. Despite variation in speeds in the rotation of the drum (L-R), the nystagmus was of a uniformly fast rate. Rotation of the drum in the opposite or R-L direction elicited a normal response in all of the animals.

2. *Complete loss or impairment of optokinetic nystagmus on contralateral rotation.* There were seven monkeys in this group. In two monkeys the electrolytic lesion in the pretectal region produced complete but transient contralateral loss of optokinetic nystagmus. When the lesion was made on the left, R-L rotation produced no response, while L-R rotation resulted in normal optokinetic nystagmus. In both of these animals there was subsequent lessening of the optokinetic nystagmus defect. Five monkeys showed a persistently defective optokinetic nystagmus of poor amplitude, although this was never completely abolished during the period of observation. One of the monkeys showed paralysis of contralateral horizontal gaze. The other four monkeys avoided looking to the side opposite to the lesion.

Lesions of brainstem with neither paresis of gaze nor optokinetic defect. In 26 monkeys a lesion, varying from 2 to 5 mm. in diameter, was made in the brainstem other than in the paramedian zone. None of these showed a paresis of lateral gaze or any defect in the optokinetic response. The lesions in this series were deliberately made in different regions of the brainstem, such as the colliculi, central gray matter, reticular formation of the medulla, brachium conjunctivum, medial lemniscus, basis pontis, and the tectospinal tract. Several lesions were placed in the vestibular nuclei, but the results have not yet been evaluated.

DISCUSSION

From the foregoing results one may conclude that lesions in specific areas of the tegmentum of the brainstem interfere with impulses for optokinetic nystagmus as well as for ocular deviations. Conversely, it may be assumed that 1) the afferent visual impulses reaching the central visual areas, such as the occipital lobe, are then transmitted along pathways projected into the brainstem in a descending direction, and 2) impulses arising from areas of the cerebrum other than the visual (that is, rostral to the occipital lobe, for there are well preserved ocular deviations in monkeys after complete bilateral occipital lobectomies) also descend and project into the tegmentum of the brainstem. Consequently, it would appear that there are at least two oculomotor pathways which project from the cerebral cortex into the paramedian zone of the tegmentum of the brainstem. Since each of these pathways subserves an oculomotor effect, one would be tempted to explain the abolition or lessening of the optokinetic response, even though the power of ocular deviation seemed to be well preserved, on the basis of separate pathways subserving different functions. This is a false assumption. If there were different pathways for specific functions,

one would also expect to find the converse of our observations, namely a loss of ocular deviation and preservation of the optokinetic nystagmus. This was never observed in our series. Single discrete lesions made in different regions of the paramedian zone never resulted in a defect or paralysis of conjugate deviation without a concomitant loss or defect in optokinetic nystagmus. As already stated, paralysis of gaze was always accompanied by a loss of optokinetic nystagmus. This impairment in optokinetic response persisted long after the power of ocular deviation returned. From the foregoing it would appear that an alteration in the optokinetic effect is an expression of defect in ocular deviation.

The question which arises from the above considerations is, at what point do the fiber pathways originating in the frontal and occipital lobes merge and integrate into one system? Does this take place in the internal capsules, pretectum, or the brainstem? The merging of these pathways and integration of function may occur in the reticular formation itself where there are numerous ganglion cells and fiber networks. It is probable that integration of oculomotor function also takes place at this level, since lesions in the paramedian zone interrupt oculomotor deviation, eye centering, and optokinetic nystagmus. It would appear from the foregoing studies that the paramedian zone is a crucial structure in the mediation of oculomotor impulses. We did not find that lesions of the median longitudinal fasciculus alone resulted in defects in conjugate ocular gaze or optokinetic nystagmus.

SUMMARY

1. The optokinetic responses of 57 monkeys were studied before and after electrolytic lesions were made throughout various regions of the brainstem. Each monkey had only one lesion.

2. A small lesion made in the paramedian zone (1 to 2 mm. from the midline) of the tegmentum of the brainstem, particularly the pons, causes an enduring paralysis of ipsilateral horizontal ocular deviation. There is also a complete loss of optokinetic nystagmus when the drum is rotated from the side of the lesion to the center of gaze. Lesions made in the more ventral portions of the paramedian zone near the basis pontis may result in transitory changes in the optokinetic nystagmus without concomitant paresis of ipsilateral horizontal eye movement.

3. Lesions in the pretectal region may cause loss or impairment of optokinetic nystagmus on the side opposite the lesion. This may or may not be associated with paresis of contralateral horizontal conjugate gaze.

4. The impulses for optokinetic nystagmus and for spontaneous deviation of eyes are mediated through a common or identical descending pathways through the brainstem. Defect in optokinetic response always accompanies defect in conjugate ocular gaze.

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Arteriographic Demonstration of Collateral Circulation in Cerebrovascular Disease

Gerard M. Lehrer, M.D.

ALTHOUGH the existence of collateral systems in the cerebral circulation other than the circle of Willis has long been known, their functional significance in maintaining the blood supply to the brain in thrombotic or embolic occlusion of major arterial trunks is not entirely clear. These connections have been described in the literature of the last century.[1,2] Lewandowsky mentioned "massive and extensive anastomoses of the pial vessels."[1] Van der Eecken and Adams[3] in postmortem anatomic studies demonstrated not only the almost constant presence of these anastomoses in the normal brain, but also found evidence of their significance in occlusion of major branches of the circle of Willis. The standard texts of anatomy mention anastomoses between branches of the ophthalmic artery and the external carotid. These have recently been reviewed[4] and their possible functional importance has been emphasized.[5–11]. Only relatively recently have reports of sporadic arteriographic demonstrations of such collateral pathways in the living patient found their way into the literature. Essentially two types of anastomotic systems have been described: 1) between the branches of the three major cerebral arteries on the surface of the brain,[12–18] and 2) between branches of the external carotid and ophthalmic arteries.[19–27] Krayenbuehl and Richter[28] claim two cases in which they demonstrate anastomoses between muscular branches of the occipital and vertebral arteries; however, the roentgenographic appearance in their illustrations may well be that of reflux from the common carotid into the vertebral artery.

We have recently had the opportunity to observe three patients with major vascular occlusions, in whom the existence of these shunts could be clearly demonstrated in serial carotid arteriograms. They are reported at this time in order to reemphasize the role of serial arteriography in the study of occlusive cerebrovascular disease.

CASE REPORTS

Case 1. A 45 year old man had no previous history of vascular disease. Following about 12 hours of premonitory symptoms consisting of headache and flashes of light in the right eye, the patient suddenly developed left hemiplegia. On examination the patient complained of severe right-sided headache. He was disoriented, unattentive, and drowsy. There was complete left hemiplegia, hemianesthesia, and left homonymous hemianopsia. The cerebrospinal fluid contained 10 white cells and 160 crenated red blood cells. An electroencephalogram showed severe right-sided and left anterior slowing. Skull roentgenograms revealed the pineal to be shifted 1 cm. to the left of the midline. The patient continued to show marked fluctuations in his state of consciousness for five days, but he was oriented when roused. Thereafter the mental status cleared rapidly, and over the next four weeks there was progressive clearing of sensory function and the hemianopsia, as well as partial return of motor function.

Right percutaneous carotid arteriograms were performed on the third day and one month after onset of symptoms. In the first arteriogram (figure 1) in the lateral view, only the anterior cerebral artery is seen to be filled in the early phases. In the later phases the anterior and insular branches of the middle cerebral artery can be seen to fill in a retrograde fashion. In the anteroposterior view (figure 2) the origin of the middle cerebral artery is not visualized and appears to be occluded. The retrograde filling of the branches of the middle cerebral artery is again demonstrated. The anterior cerebral artery is shifted 1 cm. across the midline, probably due to cerebral edema.

In the second arteriogram, performed about three and a half weeks later, the arteries are seen to be filled in their usual fashion and the arteriogram appears normal in every respect (figure 3). The anterior cerebral artery and the pineal gland have returned to their midline positions. No evidence of the previous occlusion can be found. Explanation of the reestablishment of the circulation is open to speculation.

Case 2. A 77 year old man in good general health seven months prior to admission to the hospital experienced an episode of sudden hazing of vision in the left eye which lasted five minutes and cleared completely without recurrence. During the four weeks preceding his admission the patient experienced 12 to 15 episodes of shaking of the right lower extremity and weakness in the right knee lasting about 30 to 60 seconds; the weakness cleared within about 15 minutes. Following the last of these, the patient noted numbness of the

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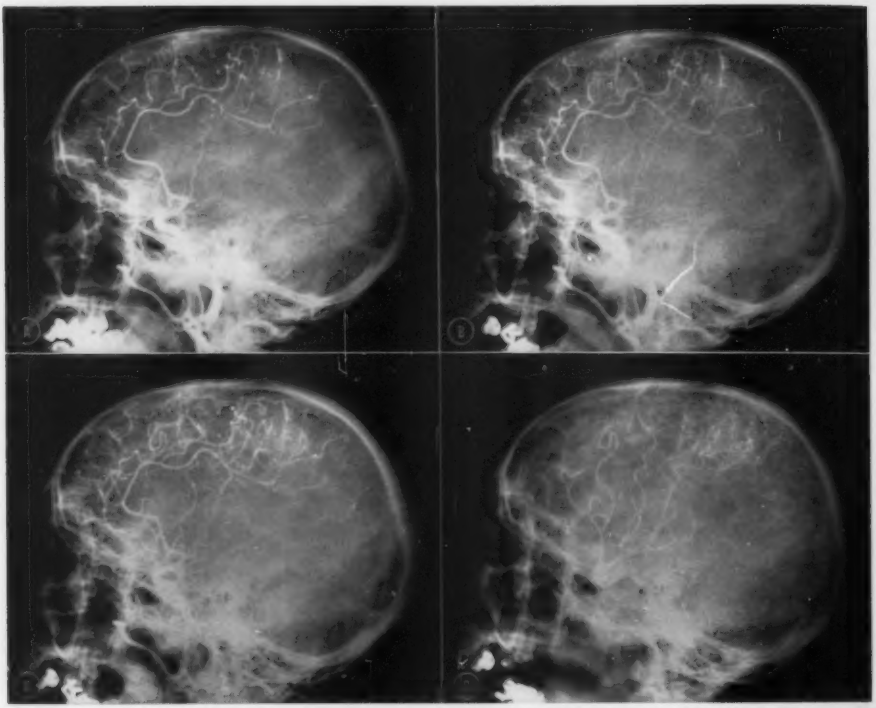

FIG. 1. *Case 1.* Right carotid arteriogram three days after onset of symptoms. *A*, *B*, *C*, and *D* are serial exposures made 3, 4, 5, and 6 seconds after injection of 10 cc. of Hypaque over the course of one second.

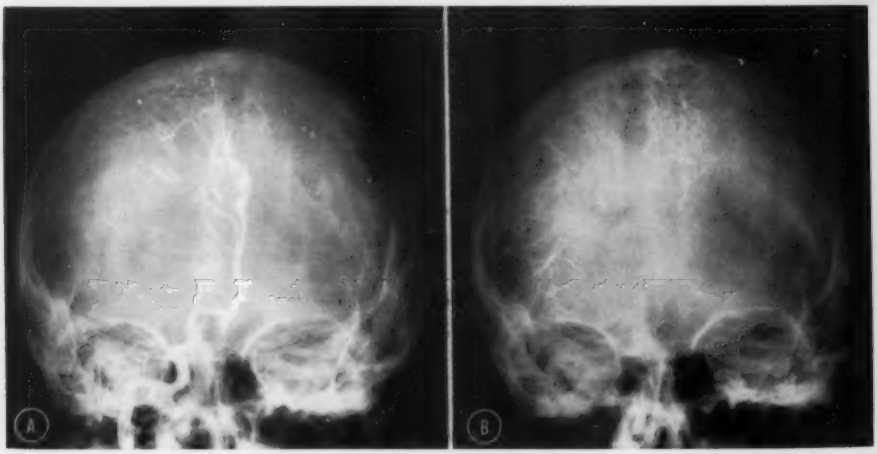

FIG. 2. *Case 1.* Anteroposterior view taken at the same time as figure 1. *A* and *B* were exposed 3 and 6 seconds after injection.

FIG. 3. *Case 1.* Right carotid arteriogram one month after onset of symptoms. *A* and *B* are lateral and anteroposterior views taken 3 seconds after injection.

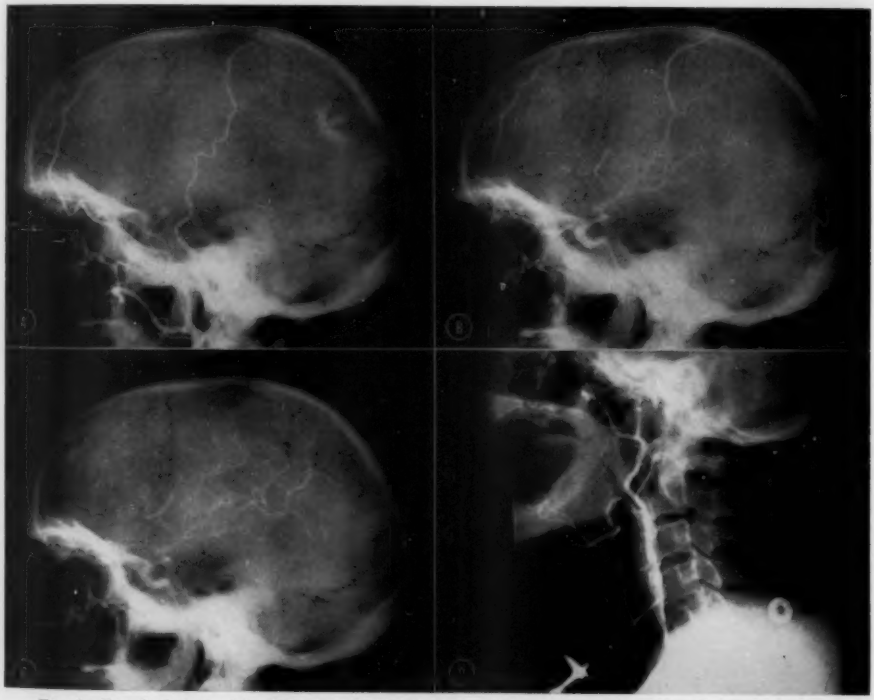

FIG. 4. *Case 2.* Left carotid arteriogram. *A, B,* and *C* are serial exposures made 3, 4, and 5 seconds after injection of 8 cc. of Hypaque. *D* is a single exposure in the lateral view during injection of 4 cc. of Hypaque.

right foot and loss of sensation of position, as well as weakness in the right lower extremity. Neurologic examination revealed only minimal weakness of the right lower extremity and minimal decrease of position sense in the toes on the right. These findings gradually cleared over the course of the succeeding week. The left carotid pulse was somewhat less forceful than the right. Electroenceph-

alogram was normal. The cerebrospinal fluid contained two cells and protein of 110 mg. per cent.

A left percutaneous carotid arteriogram was performed and revealed filling of the external carotid system (figure 4 A, B, and C). The carotid syphon may be seen to fill by way of the ophthalmic artery in a retrograde fashion. In serial films the flow of contrast medium can be traced from the anterior branch of the superficial temporal artery, through its frontal ramifications into anastomotic branches of the lacrymal artery, and thence into the ophthalmic artery. The subclinoid portion of the internal carotid artery is seen to fill in a retrograde fashion and appears markedly narrowed. The middle cerebral artery is well filled and appears normal. The anterior cerebral artery is not made out; it is likely that it derives most of its blood supply from the opposite internal carotid artery by way of the anterior communicating. A view of the carotid artery in the neck (figure 4D) shows the point of the needle in what appears to be the common carotid artery. The carotid bulb is distal to the insertion of the needle and a small irregularity may be seen in its posterior, upper portion, which is presumed to mark the origin of the thrombosed internal carotid. A pneumoencephalogram showed moderate dilatation of both lateral ventricles, slightly more pronounced on the left.

Case 3. A 70 year old left-handed woman experienced sudden onset of left-sided weakness and speech disturbance seven weeks prior to her admission to the hospital. She recovered in one week with mild residual weakness. Four weeks before admission the patient experienced sudden increase in weakness, again followed by partial recovery. The past history revealed generalized arteriosclerosis and anginal syndrome. On neurologic examination there was mild left hemiparesis, more marked in the upper extremity, without disturbances in speech or mentation. On her third hospital day the patient was found on the floor of her room, apparently having gotten out of bed to go to the bathroom. She had a severe left hemiparesis and motor aphasia, but was able to obey commands. Later that day she had left hemiplegia, with a left hemisensory sydrome and left homonymous hemianopsia. Segmental reflexes as well as Babinski and Hoffman signs could be elicited on the left. A slightly traumatic lumbar puncture showed the cerebrospinal fluid to contain three white cells, 92 red blood cells, and a protein of 28 mg. per cent. An electroencephalogram on the second hospital day (prior to the severe episode) revealed symmetric six-per-second bursts of slow activity. Over the next four days the patient showed marked fluctuations in her state of consciousness and had to be given intravenous fluids because of difficulty in taking food. Thereafter the patient improved somewhat, becoming more alert and eating solid foods. Mild aphasia and hemiplegia persisted.

A right percutaneous carotid arteriogram was performed on the fourth day after the acute episode (figures 5 and 6). The external carotid artery and its branches are well filled. The internal carotid artery is not visualized and the carotid syphon cannot be seen proximal to the point of origin of the ophthalmic artery. The flow of contrast substance can be traced from the internal maxillary artery into a large deep anterior temporal artery which appears to anastomose directly with the lacrymal artery, through the latter into the ophthalmic artery, and thence into the carotid syphon. This is most clearly seen in the anteroposterior projection. In this case the anterior cerebral artery is well filled, whereas only a few branches of the middle cerebral artery can be seen (figure 6). The origin of the latter appears to be partly occluded. The large, well defined anastomotic pathway would appear to indicate prolonged preexistence of the internal carotid thrombosis. We may speculate that the severe episode, and probably also the minor episodes, may have been due to emboliza-

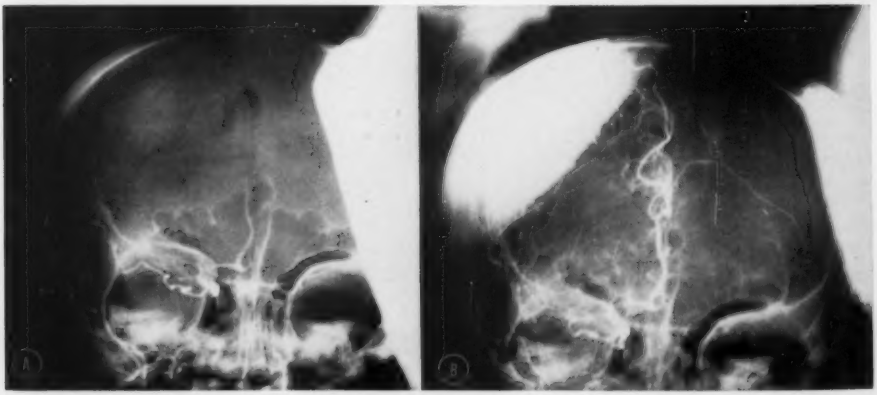

FIG. 5. *Case 3.* Right carotid arteriogram, anteroposterior view. *A* and *B* were exposed 2 and 4 seconds after injection of contrast material.

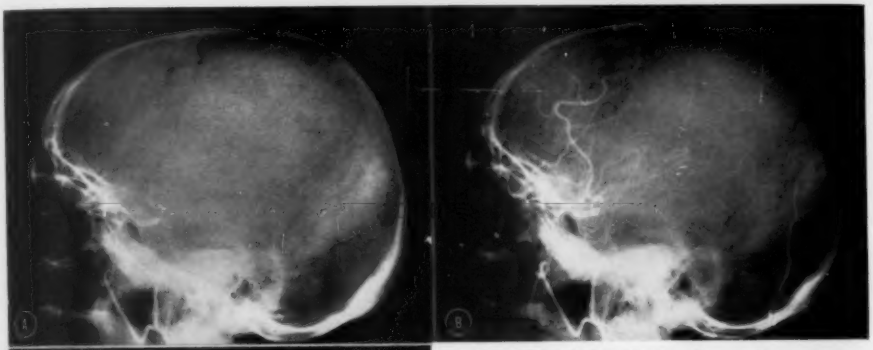

FIG. 6. *Case 3.* Lateral view taken at the same time as figure 5. *A*, *B*, and *C* were exposed 1, 3, and 6 seconds after injection.

tion of branches of the middle cerebral artery by thrombi originating from extension of the thrombus in the pre-ophthalmic portion of the carotid syphon.

SUMMARY

Three cases have been presented, one in which the functional existence of pial anastomoses between the anterior and middle cerebral arteries was shown, and two in which anastomotic pathways were demonstrated by means of serial arteriograms between the external and internal carotid system. Such arteriographic demonstrations of collateral cerebral circulation in occlusive cerebrovascular disease in the current literature were surveyed. The clinical pictures appear to indicate that these collateral pathways form an important contribution to the cerebral blood supply in the patients presented. However, the number of well documented cases at this time is not sufficiently large to permit any conclusions as to the prognostic or clinical significance of the demonstrability of collateral circulation by arteriographic means. An extensive study of clinical-arteriographic correlations in patients with occlusive cerebrovascular disease appears indicated.

The author is indebted to Drs. Morris B. Bender, Phillip Bergman, and Morton Nathanson for the use of their case material.

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■ The *exciting* or *occasional* causes of apoplexy mentioned by authors, are very numerous. Some account of them has been already given in the description of morbid appearances found within the cranium on dissection. They are chiefly blood; serum; tumours; hydatids; polypous concretions; ossifications; exostoses; and various lesions of the brain. These causes are said to act by producing pressure on the brain, which is supposed to be the most common immediate cause of the disease; and they may be divided into such as act quickly and powerfully, and those which act more gradually and feebly, in producing this pressure; the degree and the duration of the disease, being proportioned to the degree and duration of the pressure. In the strong *sudden* apoplexy, attended with stertorous breathing, the exciting cause is, I believe, almost always, an effusion of blood, because we can easily understand how by the rupture of a considerable vessel in the brain, an effusion sufficient to occasion a sudden and great pressure may take place, and because on examination after death we almost always actually find such effusion.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Seizures and Syncope

Dewey K. Ziegler, M. D. and Jan Presthus, M.D.*

SEIZURES simulating the common fainting spell have aroused sporadic interest for many years. It is well known that there is no altered state of consciousness, of whatever cause, which cannot be mimicked by a paroxysmal nervous system disorder. The seizure manifestations which tend to be confused with vasodepressor syncope are: 1) loss of postural and muscular tone (instead of the more common exaggerated tone, or movement) accompanying loss of consciousness, and 2) prominent autonomic manifestations preceding and during the episode. Both of these phenomena have been discussed separately in the neurologic literature on seizures.

Concerning autonomic phenomena in epilepsy, Gowers many years ago described cases of "vasovagal attack" in which pallor, a feeling of coldness, fear of death, and respiratory disturbances were presumably manifestations of central nervous system dysfunction.[1] Subsequently, Kinnier-Wilson summarized the numerous reported cases of episodic changes in consciousness, with pronounced visceral symptoms and autonomic manifestations.[2] More recently, Penfield and Jasper have described cases of "diencephalic epilepsy" in which autonomic phenomena were the major component of the convulsive disorder.[3]

The other element in the syncopal syndrome—loss of postural tone accompanying loss of consciousness (the "limp" fall)—has also been described as a seizure phenomenon. In elucidating the carotid sinus syndrome, Weiss and Ferris,[4,5] described an uncommon cerebral form of syncope in which pressure on the carotid sinus caused loss of consciousness in the absence of any change in pulse rate or blood pressure; it has been speculated that the carotid sinus stimulation triggers a seizure phenomenon. Syncope of neurogenic origin has also been described in various types of "akinetic" seizures, in which the individual falls suddenly and without warning.[6,7] Gastaut[8] has recently declared that he found this type of seizure to be extremely rare. Electrical stimulation of various areas of the brain, however, has repeatedly produced inhibition of motor activity in animals and man, both spontaneous and elicited by cortical stimulation.[9–12]

Over the years scattered accounts have occurred of patients who show prominent autonomic phenomena with brief loss of consciousness and of postural tone—but no convulsive movements or abnormal activity of any type—as a manifestation of central nervous system dysfunction. The difficulty in making the "fit or faint" diagnosis has recently been well discussed by Symonds and others.[13–15]

The electroencephalographic findings in patients with "simple" syncope have usually been found to be normal.[16–18] More recently, groups of cases have been described of individuals with phenomena simulating vasodepressor syncope but with prominent electroencephalographic abnormalities.[19–20] Many of these individuals have more well-defined seizures, in addition to these syncopal episodes.

The present study was undertaken to discover the coincidence of syncope and abnormal electroencephalograms to identify those atypical syncopal states which seemed to overlap with more readily recognized seizure manifestations, and to study the effect of sleep and hypoglycemic activation of the electroencephalogram in these conditions.

MATERIAL AND METHOD

In the present study an attempt was made to get a complete clinical description of "fainting spells" from patients who had such episodes fairly frequently. Patients were derived from various sources. Questionnaires were distributed to all patients attending a seizure clinic and to patients having examinations at an electroencephalographic laboratory. Patients were also obtained from a group who admitted to numerous fainting spells on questionnaires distributed to all students by a university health service. The questionnaires were then screened; those patients denying any type of movement or activity during a fainting spell were interviewed and the charts reviewed.

Twenty-three patients were used in this study. All except three of these patients denied the more familiar manifestations of grand mal, petit mal, and psychomotor seizures. The remaining three had some motor activity during the "spell" and this will be described in

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detail. Excluded were patients with severe cardiovascular disease, cardiac arrhythmia, severe anemia, and such obvious primarily nonneurologic causes of syncope.

The history included events preceding, during, and following the spell. The patient was asked whether emotional stimuli, feelings of "faintness" or dizziness, or autonomic phenomena preceded the episode. Data on the length of the episode, completeness of unconsciousness, and the frequency of spells were obtained. Occurrence of confusion or sleep following the spell was asked for. Wherever possible, an informant other than the patient was also interviewed to confirm the history.

Electroencephalograms were done on all patients, and in addition most had an electroencephalogram activated by sleep and another by insulin-induced hypoglycemia. In all patients blood pressure was recorded, and the electrocardiogram was recorded on one channel of the electroencephalograph record. Blood sugar determinations were done on venous blood by the Benedict method; normal values for this laboratory are 70 to 90 mg. per cent.

RESULTS

On the basis of clinical characteristics, we divided the patients into three groups, for which clinical and electroencephalographic data are given below.

Group A (13 cases)

Clinical Data

In this group, brief complete loss of consciousness occurred in young individuals without other etiology than fatigue, hunger, or emotion. Eight patients were under age 20, four were from 21 to 30, and one was over 30.

Twelve of these patients stated that at some time they had had an episode of complete loss of consciousness with amnesia for the period. In addition, many had episodes which seemed to them similar to "fainting spells" but in which consciousness was not lost. These episodes were described frequently as "faintness" or "dizziness," or the patient might be partially aware of surroundings. In 11 patients the length of the episode was estimated as less than five minutes, in one as between five and 30 minutes, and in one as over 30 minutes. Most of these patients had symptoms of weakness and sweating following recovery of consciousness, but few noted confusion.

None of these patients had a family history of seizures. The fathers of three of the patients were said to have syncope and in one case, a brother also.

Seven of these patients recognized some type of emotional stress preceding the syncope. All of these seven patients and four of the remaining six had some premonitory warning of syncope, such as a feeling of "faintness" or "dizziness" or autonomic changes. The usual stimulus was apprehension of pain, the well-known "sight of blood," or exhaustion from various causes.

Electroencephalographic Data

Of these 13 patients, ten showed completely normal records in the resting state. One record was borderline, showing prominent sharp activity and fast activity; a second showed some slowing on hyperventilation; the third showed some definite bursts of paroxysmal activity:

Case 1. A 21 year old housewife used to "faint" several times per week, many, but not all, of the spells being preceded by emotional disturbance and a warning of "faintness." At times the patient merely "feels faint" but does not lose consciousness. On one occasion she was said to be "rigid." Physical and neurologic examinations were negative, except for some drop in blood pressure on assuming an upright position. The electroencephalogram (figure 1) showed bursts of bilaterally synchronous 5 to 7 c/s activity, of highest amplitude in frontal regions, and associated with low voltage spike.

Sleep recording produced no further adbnormalities in any of the six patients in whom it was done.

Insulin-induced hypoglycemia has been reported to be effective in eliciting abnormalities in electroencephalograms of some epileptics.[21] Therefore, a standard insulin tolerance test was done on ten of these 13 patients, using 0.1 unit of insulin per kilogram of body weight intravenously. Electroencephalographic slowing was rated arbitrarily as minimal, moderate, or marked, as compared with the resting record. Marked slowing consisted of a record with predominantly high voltage, 1 to 4 c/s frequencies. In no case did hypoglycemia of fairly marked degree precipitate seizure, syncope, or a "classical" 3 per second spike and wave pattern. In two patients, however, definite bursts of paroxysmal abnormality were elicited by hypoglycemia, occurring in both cases 30 minutes after injection of insulin.

Case 2. A 21 year old student nurse has for several years had about two or more syncopal episodes per year, preceded by pallor, nausea, vomiting, and a feeling of faintness and dizziness, frequently precipitated by fatigue, but almost never by emotion. After fainting, the patient is weak and perspiring, not confused. Physical and neurologic examinations were normal. Chest roent-

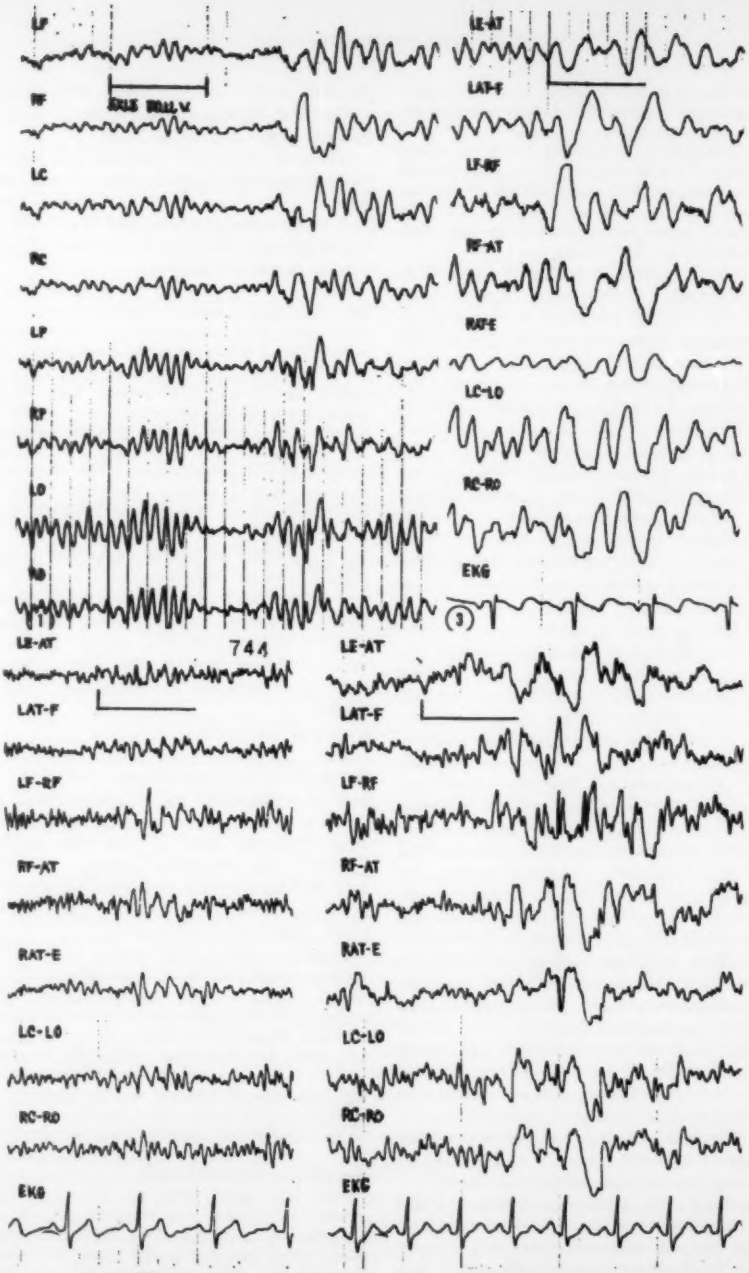

FIG. 1. *Case 1.* A 31 year old female. Calibration 50 μv., 1 sec. Electrodes connected to linked ear electrodes, no ground.

FIG. 2. *Case 2. A.* A 21 year old female, immediately after three minutes of hyperventilation. Blood sugar 84 mg. per cent. Calibration, 50 μv., 1 second. *B.* 30 minutes after intravenous injection of 6 units of crystalline insulin, and after 100 seconds of hyperventilation. Blood sugar less than 15 mg. per cent. Calibration, 50 μv., 1 second.

FIG. 3. *Case 1.* A 31 year old female, 30 minutes after intravenous injection of 7 units of insulin. Blood sugar less than 15 mg. per cent. Calibration, 50 μv., 1 second.

genogram revealed a large anomalous pulmonary vein and slight right-sided heart enlargement. Resting electroencephalogram showed only questionable abnormality, consisting of some sharp waves (figure 2A). The electroencephalogram after three minutes of hyperventilation during severe hypoglycemia produced by insulin contained a paroxysmal burst of bifrontal spike and slow wave dysrhythmia (figure 2B).

The second patient with extreme electroencephalographic response to hypoglycemia was the one with an abnormal resting electroencephalogram whose case has been described (case 1). The record during hypoglycemia, before hyperventilation, shows bursts of high voltage delta (2 to 3 c/s) activity from all areas (figure 3).

In four additional patients hypoglycemia precipitated moderate to marked slow abnormality. In an additional two patients minimal slowing occurred. Hyperventilation for three minutes during hypoglycemia induced moderate to marked electroencephalographic slowing in only three patients.

Group B (5 patients)

Clinical Data

The second group of patients described typical syncopal episodes, but had some other medical condition which might have been responsible for either syncope or seizure, the differential diagnosis being extremely difficult. The diagnoses on these patients were as follows: 1) Arteriosclerosis with abdominal aortic aneurysm. 2) History of transient hemiplegia eight years previously and also of head trauma with residual visual field defect. Convulsions in childhood. 3) Gastrectomy for peptic ulcer three years before admission. 4) Temporal lobectomy for psychomotor seizures one year previously. 5) Diffuse demyelinating disease. Two of these patients admitted to emotional precipitation of episodes and one claimed fatigue as a cause. Three patients had premonitory warnings of syncope in the nature of feelings of dizziness or faintness. All except one described brief and complete losses of consciousness with falling; the exception was the patient with a history of hemiplegia who described episodes lasting one-half to one hour consisting of extreme faintness and dulling of perceptions and usually relieved by eating.

The patient with a temporal lobectomy had had one focal motor seizure in addition to syncope; the patient with demyelinating disease had had postpartum seizures 20 years previously.

None of these patients had hypertension or anemia. In one patient the electrocardiogram showed bundle branch block with premature ventricular contractions.

Electroencephalographic Data

Three of these five patients had abnormalities of moderate degree, one record showing diffuse slow abnormality, a second diffuse fast and sharp wave activity, and the third paroxysmal bursts, asymmetric in nature. This third case is described below:

Case 3. A 33 year old male suffered transient left hemiplegia with complete, rapid recovery eight years prior to examination. Subsequently, he suffered head injury with unconsciousness and has residual visual field defect. Once or twice a month, usually in the setting of hunger and fatigue, he suffers spells of extreme weakness, "faintness" and dulling of consciousness, preceded by pallor, sweating, and dizziness. It is doubtful that he has ever completely lost consciousness. The electroencephalogram showed definite paroxysmal spike and slow wave bursts, chiefly right sided, probably focal (figure 4).

Of the other two patients in this group, the elderly woman with arteriosclerosis had a normal record and the post temporal lobectomy patient showed slight diffuse abnormality. Sleep activation was done on two patients and insulin-induced hypoglycemia on another two with no additional abnormalities being produced.

Group C (5 cases)

This group of individuals suffered from states of altered consciousness which were not typical syncope but which are included in this study because they are difficult to differentiate from "fainting" and do not fall easily into known types of seizure patterns, although it was our feeling that probably all these manifestations were seizures. Brief case reports are given below.

Case 4. A 56 year old woman had had, for 30 years, frequently in the premenstrual period, spells usually precipitated by emotion and preceded by pallor, dizziness, and a feeling of faintness and of a "white cloud" being drawn before her eyes. A few times she had been completely unconscious, but states she can usually understand what is being said around her but cannot answer. These episodes lasted from a few minutes to almost an hour and left the patient pale, perspiring, and weak. No movements were ever noted, nor had the patient injured herself. In recent years the patient had some moderate depression and insomnia for which she received electric shock. Electroencephalograms done during waking and sleep states, before electric shock, revealed only questionable diffuse abnormality consisting of runs of low voltage fast activity.

Case 5. A 16 year old boy had a history of subarachnoid hemorrhage and ventriculogram five

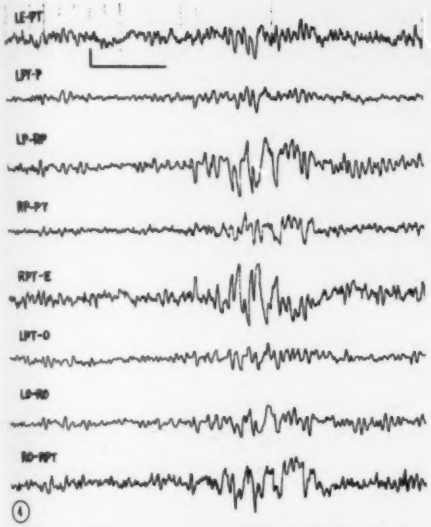

FIG. 4. *Case 3.* A male 33 years old, awake. Blood sugar 73 mg. per cent. Calibration, 50 μv., 1 second.

years before examination. He had had two episodes of sudden dizziness, followed by falling and unconsciousness. He was limp, but one witness said there were a few tremors of feet and arms. On one occasion there was a feeling of faintness but no autonomic manifestations. The electroencephalogram showed high voltage bifrontal slow wave bursts at 2 to 4 c/s (figure 5).

Case 6. A 59 year old woman with almost daily attacks lasting 30 to 90 minutes, with weakness, inability to speak, and altered state of consciousness brought on frequently by disgust, anger, or fright and preceded by a peculiar feeling in the chest and abdomen. Falling frequently is a part of the episode, as is a head tremor; the patient is partially amnesic for the spell. Electroencephalograms showed borderline diffuse sharp head abnormality. There had been numerous episodes of head tremors in the past. This patient had had a pneumoencephalogram (negative). The "spells" were greatly diminished in number by Dilantin therapy.

Case 7. An 18 year old girl has numerous typical syncopal spells, not precipitated by emotion but preceded by pallor, nausea, sweating, and a feeling of faintness and dizziness. The episodes last one or two minutes, and observers say she has occasionally some irregular movements of the limbs, not clonic in type. There is no incontinence or tongue-biting, and following the episode she feels "cold." Electroencephalograms during waking, drowsy, and hypoglycemic states were normal. Her father has syncopal episodes not diagnosed as seizures.

Case 8. A 22 year old woman has had numerous episodes since adolescence, always precipitated by emotion, in which she falls limp and loses consciousness for a few seconds to several minutes. These are usually not preceded by faintness or autonomic phenomena, although on a few occasions she has had transient feelings of faintness. The patient came from a turbulent environment and had made a suicidal attempt. She received fairly prolonged psychotherapy. Electroencephalograms revealed bilaterally synchronous runs of 6 c/s activity with some slower activity in frontal regions (figure 6).

GENERAL COMMENT

This study was undertaken in an attempt to determine the incidence of electroencephalographic abnormality in a group of patients with the complaint of episodic loss of consciousness in the absence of an identifiable history of well-known manifestations of seizures. A large group of these patients, mostly young women, suffered from syncope usually precipitated by emotion and preceded by autonomic manifestation. It is worthy of comment, however, in describing the difficulty in differentiating seizures from syncope, that several of these patients did *not* describe preceding stressful phenomena. All except one of these cases showed a normal electroencephalogram, and syncope was presumably vasodepressor in origin, that is, a result of failure of cerebral circulation due to drop of blood pressure. In these cases there is the well-known sequence of clinical events seen in "fainting"—namely, dizziness, blurred vision, pallor, and sweating, followed by loss of consciousness and postural tone. Symonds[14] suggests that even in such cases the "triggering" of the faint is a central nervous system phenomenon and may indicate some brain pathophysiology. We had speculated that if this were so, either sleep or hypoglycemia might precipitate electroencephalographic abnormalities in these patients. In one patient with a questionably abnormal resting record, hypoglycemia (at a blood sugar level less than 15 mg. per cent) did produce a definite paroxysmal abnormality (figure 2). It may be speculated that patients showing such a response to hypoglycemia also have a low convulsive threshold, much as the patients who have seizures during insulin coma treatment. Such an electroencephalogram, however, proves nothing about the nature of the fainting spells at a normal blood sugar level.

There are cases in which the spells are clinically indistinguishable from those described above, but show striking abnormalities in nonactivated electroencephalograph records. There

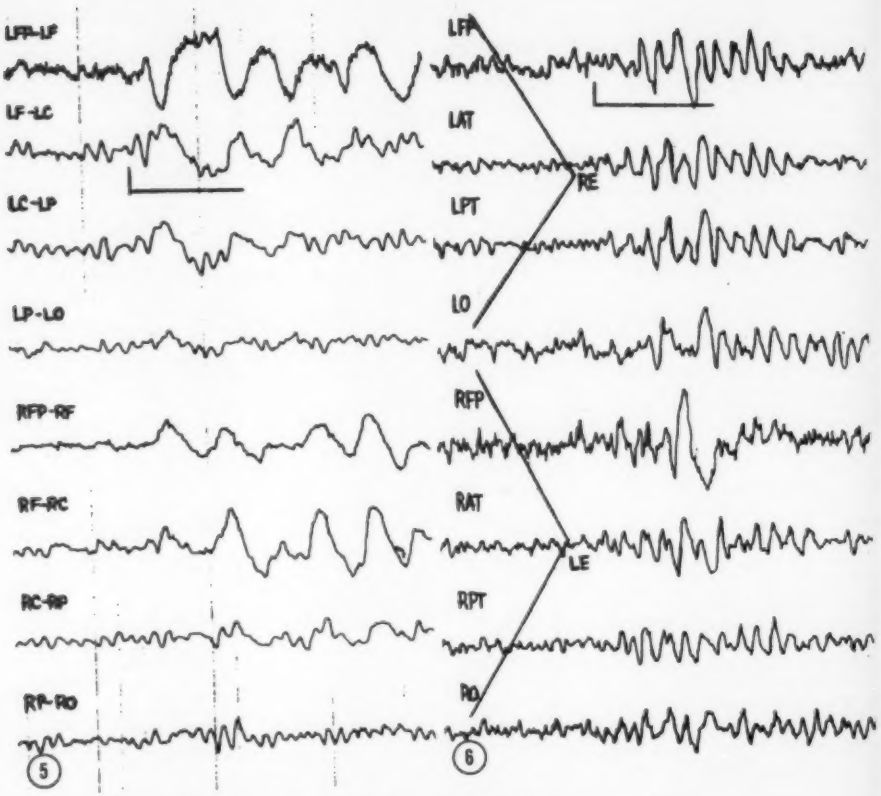

FIG. 5. *Case 5.* A 16 year old male, awake. Calibration, 50 μv., 1 second.
FIG. 6. *Case 8.* A 22 year old female, awake, non-fasting. Calibration, 50 μv., 1 second.

were three such patients in our series whose syncope frequently occurred without any emotional precipitation and without premonitory signs or symptoms.

Just as absence of emotional precipitation of syncope is not predictive of electroencephalographic abnormality, neither is absence of autonomic phenomena, since two patients with normal electroencephalograms had fainted without warning or preceding autonomic phenomena.

The problem is whether electroencephalographic abnormalities in patients with syncope indicate that the latter phenomenon is a seizure; this question is insoluble unless one of the patient's typical "spells" is observed during an electroencephalogram. At least some episodes of simple loss of consciousness and postural tone, even though preceded by autonomic and emotional phenomena, are of epileptic etiology. Such cases have some characteristics of the "akinetic" epilepsy and also of the ill-defined group of "visceral" epilepsies. Autonomic manifestations, so common in simple fainting, are also a frequent accompaniment of seizures originating in various brain areas.[22]

It is well known that abrupt changes in blood pressure and other autonomic effects can be produced in man and in animals by electrical stimulation of various parts of the cerebral cortex — notably different areas of the temporal lobe, insula, and the cingulate gyrus.[23–25] It is not surprising then that seizure states may also begin with striking autonomic changes that may mimic emotionally caused syncope.

The second and third groups of patients in

this study are included to emphasize the frequent difficulty encountered in distinguishing, in a patient complaining of syncope, between a seizure state, simple syncope, and a variety of other conditions causing sudden loss of consciousness. In the second group, the syncope described was typical and indistinguishable from that described in group one. Three of these patients, however, showed abnormal electroencephalograms – one case (figure 4) with a history of probable cerebrovascular accident, a second with demyelinating disease, and a third with a history of gastrectomy. The history of neurologic disease associated with electroencephalographic abnormality strongly suggests seizures in at least the first two. In the fourth patient of group 2, also, syncope probably was a form of seizure, since it occurred with great frequency following a temporal lobectomy and was almost completely eliminated by Mesantoin therapy. Taking electroencephalographic and clinical data together, therefore, three out of five of these patient probably suffered seizures.

The third group of cases included those in which the altered state of consciousness was not typical of simple syncope and yet not easily recognizable as a seizure. There were cases in elderly patients of fairly prolonged states of altered consciousness, sometimes unconsciousness often followed by neurologic signs such as head tremor or ataxia. In two cases some rigidity or a few clonic movements had been noted with the faint; these do not in themselves establish the diagnosis of seizures, since they will occur rapidly after the onset of unconsciousness in any condition in which the brain is made anoxic. An interesting possibility is that these prolonged states of semiconsciousness in elderly individuals may represent periods of partial cerebral anoxia in individuals with arteriosclerotic cerebrovascular disease. Meyer and co-workers have recently demonstrated that postural tilting can cause relative hypotension and electroencephalographic changes, and conclude that other similar but more prolonged and severe drops in blood pressure may produce syncope or seizures.[26]

Electroencephalographic data on this third group revealed definite paroxysmal abnormality in two, borderline abnormalities in two, and normal record in one.

Some comment might be made on the use of hypoglycemia as an activating procedure. In our experience it was productive of clearly epileptiform abnormality in the electroencephalogram in only one case in the entire series and never precipitated syncope, despite extremly low blood sugar levels. In fact, the absence of any slowing, even after hyperventilation in the presence of low blood sugar values, was surprising and will be reported in detail elsewhere.

Several of these cases had fairly obvious emotional disturbances and had received psychiatric care. The relationship of syncope to emotional disturbance is probably extremely complex and not elucidated by the fairly common practice of diagnosing any conjunction of physical symptoms and mental disturbance as "hysteria." One of the cases in this series who was thus diagnosed and was receiving psychiatric care showed paroxysmal abnormalities in the electroencephalogram (figure 6). Records differing from the normal have been obtained by Gastaut in some hysterics;[27] this fact suggests physiologic disturbance in at least some of these patients, and points up the need for using combined neurologic and psychiatric technics in the study of such patients.

SUMMARY AND CONCLUSIONS

1. Clinical and electroencephalographic data are reported on a series of 23 patients subject to some type of syncope not easily recognizable as a seizure state.

2. Patients were divided into groups of a) typical syncope with no etiology known other than emotional, b) typical syncope in patients with other organic disease, and c) "atypical" syncope.

3. Definite abnormality of resting electroencephalogram was found in one out of 13 patients in group 1, three out of five patients in group 2, and two out of five patients in group 3.

4. Sleep activation produced no additional abnormalities. Insulin-induced hypoglycemia of marked degree produced in one patient of group 1 a definitely abnormal electroencephalogram, consisting of a spike and wave pattern. There is no indication from this study that there is an "unstable" nervous system or excessive susceptibility to stress (as represented by hypoglycemia) of most patients subject to emotionally produced syncope.

5. Emotional stimuli, feelings of faintness, dizziness, and autonomic manifestations preceding syncope do not reliably distinguish vasodepressor syncope from epileptic syncope; they were common but not universal in the group without electroencephalographic abnormalities. Conversely, they occurred in cases showing

prominent electroencephalographic abnormalities.

6. It is suggested that, when a phenomenon appearing to be vasodepressor syncope occurs in patients with organic nervous system disease, one should seriously consider the possibility of a convulsive disorder. The similarity of some seizure states to syncope is emphasized and the difficulty in differential diagnosis is discussed.

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■ Epilepsy is a complaint which is often accompanied with very extraordinary symptoms and circumstances, and has therefore, at all times, particularly attracted the attention both of medical men and of the world at large. It has been described by Hippocrates, Galen, Aretaeus, and all the ancient Greek physicians with whose works we are acquainted; by Celsus and other Latin authors; and by the most distinguished among the moderns; yet its nature or proximate cause still remains unknown, and the method of its cure difficult and uncertain.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Berry Aneurysms of the Circle of Willis

Results of a Planned Autopsy Study

Jacob L. Chason, M.D. and William M. Hindman, M.D.

RECENT aggressive surgical approaches in the treatment of ruptured berry (saccular, congenital) aneurysms of the circle of Willis have accompanied the use of angiography in their diagnosis and localization. Differing opinions still exist, not only between those who advocate medical therapy rather than surgical, but also within the latter group regarding the time for visualization and the exact type of surgical treatment.[1–3] Resolution of these conflicting opinions with the development of more rational conclusions may be achieved only with a more complete and accurate understanding of the natural history of this disorder. It is our belief that much of the lack of agreement stems from unevaluated conclusions derived from selected series of patients forming clinical and autopsy groups that were not completely comparable.

Statistical incidences and morphologic findings from autopsy series have varied as much as those forming clinical reports.[4–10] This has been due in part to inaccuracies that follow retrospective analysis of protocols rather than a direct and controlled thorough examination of the anatomic material from the onset of the investigation. Variations in the latter type of study can and should be minimized by the adoption of acceptable and rigid criteria prior to the analysis. The final conclusions must also take into consideration the type of hospital, its patient population, the percentage of autopsies done, and the number that include examination of the system under analysis.

The content of this report has been derived from 2,786 consecutive necropsies at the City of Detroit Receiving Hospital, the major adult emergency hospital for this city. During this period there were a total of 2,870 autopsies, representing 60.5 per cent of all deaths. The central nervous system, including brain and spinal cord, was originally examined in each case by one of the authors with but few exceptions. The routine examination always included a search for the presence of saccular aneurysms in the vessels of the circle of Willis and its branches external to the brain. An aneurysm of this type was considered to be present only if the following criteria were satisfied. It must have been represented as a local dilatation one millimeter or more in diameter when the adjacent arteries were held in their approximate antemortem position. This was done to avoid the inclusion of nonaneurysmal bulges that are occasionally seen between the wrinkles in fixed cerebral arteries and to avoid other irregularities that might occur in the outer walls of these vessels. Although it was originally decided to exclude aneurysms with more than a minimal degree of atherosclerosis in their wall, this never became an important consideration. Doubtful cases were always omitted.

The usual reported incidence of berry aneurysms at autopsy has ranged between 0.5 and 1.5 per cent.[9] These figures, in general, represented estimates derived from reviews of protocols. The direct examination at autopsy of 1,437 consecutive brains reported by Riggs and Rupp[5] disclosed a 9 per cent incidence of these aneurysms 0.5 cm. or less in diameter. Included within the 2,786 autopsies in our series are 137 patients with berry aneurysms, an incidence of 4.9 per cent.

Table 1 contains information relating the number of autopsies in each decade with the number of patients having ruptured and unruptured aneurysms. The age of the patients with the aneurysms ranged from 25 to 87 years, with a mean of 57 years. The mean age of the 57 patients with ruptured aneurysms was 54 years; in the 80 with unruptured aneurysms the mean age was 64 years. The absence of berry aneurysms in individuals in this series under the age of 25 is, in part, due to relatively few emergency pediatric cases and in part to the composition of the group under age ten. This age group was formed almost entirely by premature but legally viable infants on whom autopsy examination was almost routine and in whom aneurysms are known to be exceedingly rare.[9]

One hundred and ninety-six saccular aneurysms were found in the 137 patients (table

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TABLE 1
INTRACRANIAL BERRY ANEURYSMS FOUND AT AUTOPSY

Age	Number of Autopsies	Number of Patients with aneurysms Unruptured	Ruptured	Total
0 to 10	203	0	0	0
11 to 20	22	0	0	0
21 to 30	75	1	2	3
31 to 40	253	6	11	17
41 to 50	397	12	11	23
51 to 60	530	16	14	30
61 to 70	643	24	17	41
71 to 80	466	12	2	14
81 and over	187	9	0	9
Age not known	10	0	0	0
Totals	2,786	80	57	137

2). The presence of two or more aneurysms in 43 individuals is equivalent to an incidence of multiplicity of 31.4 per cent. Moreover, bilateral involvement of the circle of Willis was found in 19 per cent of the entire group of patients (60 per cent of those with multiple aneurysms). These findings are to be compared with other reports of multiplicity of 15 per cent and 21 per cent[9] and of bilaterality of 0.8 per cent,[4] 4.6 per cent,[9] and 33 per cent.[10]

It has been stated on many occasions that females are more frequently affected than males,[4,8,9] but the actual difference is hard to evaluate from the number of patients reported. In this series there were 60 males and 77 females with saccular aneurysms. The actual difference between the sexes is masked, however, unless one considers the ratio of the sexes in the entire autopsy population. The 2,786 autopsies include 1,718 males and 1,068 females. The actual incidence of aneurysms as to sex in this series is 3.5 per cent in males and 7.2 per cent in females. No significant difference between the sexes in the proportion of ruptured and unruptured aneurysms was noted. Although some authors have reported a higher incidence of these aneurysms in the colored race, there was no significant racial difference in this series.

The anterior half of the circle of Willis, formed by the intracranial portion of the internal carotid arteries, the middle cerebral, the anterior cerebral, the anterior communicating, and the first portion of the posterior communicating arteries and their branches, is said to be affected approximately six times as frequently as the posterior half of the circle. In our material, in spite of a diligent search, the predominance of anteriorly placed aneurysms was even greater. The anterior half of the circle was affected 177 times, the posterior half 19 times. The frequency with which these arteries were involved included the internal carotid proximal to the posterior communicating—16, at the junction with the posterior communicating artery—18, with the middle cerebral artery—23, and with the anterior cerebral artery—six. There were 53 aneurysms on the middle cerebral artery and 61 involving the anterior communicating artery. The remaining 19 aneurysms affected the vertebral-basilar artery system and its branches. The right and left sides of the circle were involved with equal frequency. The average size of the ruptured aneurysms (8.6 mm.) was almost twice that of the unruptured (4.7 mm.). There was no significant difference in size between the sexes.

TABLE 2
TOTAL NUMBER OF BERRY ANEURYSMS

94	patients	with 1	aneurysm	=	94
32	patients	with 2	aneurysms	=	64
8	patients	with 3	aneurysms	=	24
1	patient	with 4	aneurysms	=	4
2	patients	with 5	aneurysms	=	10
137	patients		aneurysms	=	196

The only illness that some have considered to be of etiologic importance in this disorder is hypertensive cardiovascular disease. It was diagnosed clinically or at autopsy in almost 80 per cent of these patients with unruptured as well as ruptured aneurysms. Congenital anomalies such as polycystic renal disease and coarctation of the aorta, reported by some as occurring with unusual frequency in patients with these so-called congenital cerebral aneurysms,[9] have not been noted in our series. In our opinion, the association of these anomalies with arterial hypertension may be the factor leading to the coincidence of these aneurysms with the two congenital abnormalities.

Fatal rupture of aneurysms (almost always at the apex) was followed by diffuse subarachnoid hemorrhage in 51 patients and by a localized hemorrhage in six. There were only nine instances in which no further complications occurred. Hemorrhage from the rupture site extended into the adjoining brain in 38 patients and into the adjoining ventricle in 20 of this group. Brainstem hemorrhages found in 15 cases occurred in five as the only complication. In three cases the complicating lesion was recent subdural extension of the subarachnoid bleeding. Death on two occasions appeared to follow the occurrence of a large and

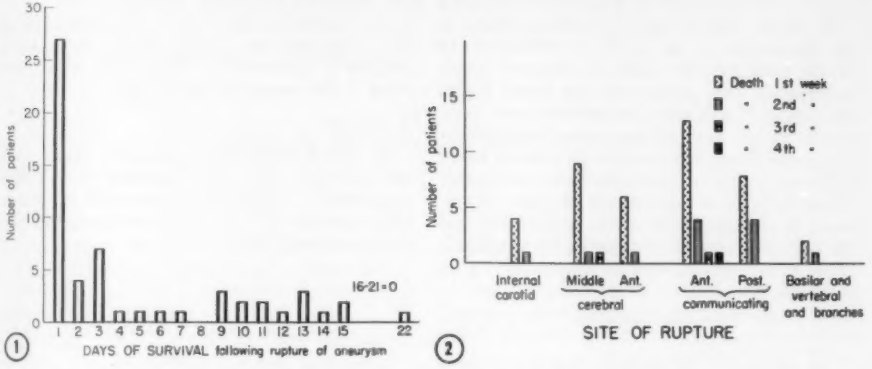

FIG. 1. Duration of survival following fatal rupture of aneurysm in patients receiving only medical treatment.
FIG. 2. Relation of site of rupture to time of death in weeks.

recent infarct in the area supplied by the major artery giving rise to the aneurysm.

Duration of survival following fatal rupture of the aneurysms in these patients who received only medical treatment is shown in figure 1. The high incidence of early death in this series as compared with others[11–13] may be attributed in part to the emergency nature of the hospital and in part to the fact that patients of this type only infrequently become part of a clinical series. In many succumbing after a week of hospitalization, death was preceded by an episode that suggested renewed bleeding. Figure 2 relates the sites of rupture with the numbers of patients and the times of death in weeks.

Several theories have been proposed as explanations for the pathogenesis and the morphologic appearance of these lesions. Forbus[14] was the first to demonstrate an initial congenitally predisposing abnormality that had previously been suggested by Eppinger[9] and by Turnbull.[15] This abnormality consisted of a defect in the formation of the media at the inner angles of the branchings of the cerebral arteries. Tuthill[16] considered the defect to be an embedding artefact. These observations of Forbus, later confirmed by others, are now generally accepted. Bremer[17] and Padget[18] were also impressed by numerous transitory arteries formed in the early development of the circle of Willis. It was the opinion of these investigators that incomplete involution of these embryonic arteries could result in points of medial weakness capable of leading to the later formation of saccular aneurysms not at bifurcations. A second and essential factor in the genesis of aneurysms is the absence of the elastic tissue normally concentrated in the internal elastic lamina. Forbus postulated that this loss was due to constant overstretching of the wall. Bremer, on the other hand, believed that transmission of a pulsatile pressure was the stimulus for the formation and maintenance of the elastic tissue and, further, that these pulsations were absent in the regions of the aneurysms. Atherosclerosis has been suggested by others as a superimposed factor leading to the destruction of the internal elastic lamina; they have, therefore, classified these aneurysms as atherosclerotic in nature. With this group one may include Walker and Allegre,[19] who were of the opinion that occluding degenerative disease of the vasa vasora of the cerebral arteries resulted in the destruction of the elastica and weakening of the arterial wall. Handler and Blumenthal[20] have repeated a previously rejected suggestion[14] that an inflammatory component was etiologically important in the development of these lesions. Another group of individuals have expressed the opinion that an added but as yet unknown factor is essential to the destruction of the internal elastic lamina.[6]

All of the aneurysms in this series have been examined with multiple sections and stains. Our findings are in agreement with those of Forbus,[14] Bremer,[17] Padget,[18] and Richardson and Hyland.[6] No evidence was found to suggest that the integrity of the internal elastic lamina was dependent upon the relatively few vasa vasora. Cellular infiltrations in and about the walls of aneurysms, as noted by Forbus[14] with whom we agree, appear to represent a reaction to, rather than the cause of, the degenerative changes within the aneurysm wall.

In 1938 Slany[21] reported abnormalities in the formation of the circle of Willis in 14 of 26 patients who died of ruptured berry aneurysms. This association was noted earlier by Padget.[18] Abnormal formations were present in 85 per cent of the cases described by Riggs and Rupp,[5] in contrast to a much lower incidence in patients without these aneurysms. These findings, if correct, are of great significance in determination of the availability and the type of surgical therapy to be employed. In our material, variations in the formation of the circle did not appear to be appreciably greater in incidence in those with aneurysms than in the nonaneurysm group.

SUMMARY

In 2,786 consecutive autopsies, there were 137 patients with berry (saccular or so-called congenital) aneurysms of the circle of Willis. The statistics for this series are presented and compared with others.

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■ Pathology is, of course, now well taught in hospitals. But I am urging that a man should go on learning pathology for himself — go on being a student as long as possible. Most of the work on pathology will be done by those who have large and special opportunities. Scientifically I am a democrat, and should like everyone to be a pathologist for himself, so far as possible. Many a man learns quickly, and is very zealous when a student; he is, apparently, a man of promise, and then stops short and ceases to improve. Every man should be original. He may make no discoveries; that is to a great extent a matter of chance. I mean that he should think for himself. If he does not himself make post-mortem examinations, he will have no trustworthy materials for such thinking on cases of living people. It is one thing to possess knowledge, and quite another thing to be possessed by that of other people.

J. Hughlings Jackson in *Address on Pathology*, published in 1882.

Effect of Diamox on Intracranial Pressure and Blood Volume

James R. Atkinson, M.D. and Arthur A. Ward, Jr., M.D.

THE EFFECTS of Diamox (2-acetylamino-1,3,4,-thiadiazole-5-sulfonamide; acetazolamide), a carbonic anhydrase inhibitor, on pressure and volume in the cerebrospinal fluid[1–3] and on the intraocular fluid systems[4,5] have been described, but the mechanism of action of Diamox on these systems is not completely understood. While Diamox is a potent carbonic anhydrase inhibitor, Maren[6] has pointed out that the strongly alkaline nature of the sodium salt of acetazolamide is a factor obscuring the effects of the drug since 50 mg. per kg. of Diamox, intravenously, produces a detectable alkalosis.

Kister[2] has shown that, while Diamox reduces cerebrospinal fluid formation in an open system, the substituted acetazolamides with reduced carbonic anhydrase activity have little effect on cerebrospinal fluid production. The possibility that this drug may gain direct access to the carbonic anhydrase within the cells is suggested by the parallel between the anticonvulsant activity of Diamox in mice and drug levels in brain homogenate.[7] Tschirgi, Frost, and Taylor[1] found that 150 mg. per kg. of Diamox intravenously reduced cerebrospinal pressure and rate of production in cats and rabbits. Using the same dose and route of administration, Knopp, Atkinson, and Ward[3] found that Diamox rapidly increased cerebrospinal fluid pressure in cats and monkeys, the pressure returning to normal levels within an hour.

It is known that the vascular dilatation accompanying elevated carbon dioxide tension results in elevated cerebrospinal fluid pressure. Diamox, by inhibiting carbonic anhydrase and thus diminishing the rate of carbon dioxide fixation as sodium bicarbonate, could conceivably produce an elevation in pressure by this mechanism. The purpose of the present study was the investigation of this possibility.

The study of cerebrospinal fluid pressure as a function of intracranial vascular volume is a problem which would ideally consider the volumes of at least three compartments (blood, brain, and cerebrospinal fluid) and the rate of transfer of fluid between these compartments. In a study such as this, where the pressure of one compartment (cerebrospinal fluid) is changing, the hydraulic impedances between compartments should be considered. Unfortunately, few of these parameters are known or available for ready observation. Studies of turnover rates in systems of hydraulic pools out of dynamic equilibrium[8] suggest that the concept of dynamic equilibrium has probably been overstressed in attempts to make precise rate determinations. Interchange of fluids between intracranial compartments may be achieved by filtration, diffusion, or little understood active transport processes which discriminate between substances presented to the "barriers." Work by Friedemann and Elkeles[9] in 1931 showed that the blood-brain barrier is permeable to basic dyes and the blood cerebrospinal fluid barrier is permeable to acidic dyes. The ready passage of lipoid soluble compounds across the blood-brain barrier is well known. The advent of isotopes has now provided a new tool for the study of barrier phenomena. Deuterium oxide has been shown to equilibrate readily with water within the intracranial systems, but common ions penetrate the barriers very slowly.[10] The use of radioactive isotopes in the study of various mammals seems to indicate little or no difference in the barrier for ions in man, apes, and commonly used laboratory animals such as cats and rabbits.[11] In some respects at least, the permeability of the blood-brain barrier is similar to that assumed for the cell membrane.[12] It would not be surprising if a drug such as Diamox, which has a pK of 9.1 as its sodium salt,[6] rather low molecular weight, and which inhibits an intracellular enzyme system, should have some marked effects on blood-brain barrier phenomena.

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The in vivo determination of intracranial blood volume seemed to be a quantity most readily estimated by radioisotope technics. To this end, readily available radio-iodinated human serum albumin (RIHSA), which has been shown to remain in the blood stream of both animals and man for prolonged periods,[18] was used. The chief problems in the present study was the development of a technic by which radiation emitted from blood in the intracranial contents could be used to estimate intracranial blood volume. Radioisotopes have also been used to study blood volumes in representative portions of the musculoskeletal system[15] and for the study of total blood volume.[16]

MATERIALS AND METHODS

Eight adult cats were used, four for the measurement of cerebrospinal fluid pressure and intracranial blood volume and four for various control experiments. Intraperitoneal sodium pentobarbital was used for anesthesia (35 mg. per kg.). The body of the animal was placed in a tunnel constructed of five-eighths inch lead slabs and the head held in position with a clamp so that the widest part of the head was in contact with a one-half inch collimating hole through a lead brick 60 mm. thick. A thallium-activated sodium iodide scintillation detector was mounted beneath the collimator, shielded from radiation from the cat by the tunnel everywhere except through the collimator. The surface of the crystal was covered with an aluminum disk 0.016 inches thick. A conventional well counter was used to measure the level of radioactivity of various fluid samples. Cerebrospinal fluid pressure was monitored with a water manometer connected through plastic tubing to a modified 20-gauge spinal needle inserted into the basal cistern.

Following anesthesia, approximately 100 microcuries of RIHSA were injected intravenously, and one-half hour allowed for equilibration of the isotope throughout the vascular system. In the following discussion, "counts" shall mean "counts per minute minus background count." Cerebrospinal fluid pressures and scintillator counts from the head were then taken during a one-half hour control period. Following the intravenous injection of Diamox (150 mg. per kg.), scintillator counts and cerebrospinal fluid pressures were taken every minute for the first ten minutes, every two minutes for the next ten minutes, and every five minutes for the next 40 minutes. Blood samples were drawn before the administration of Diamox and at the end of one hour for the determination of total blood volume by a method described later. The animal was then sacrificed by wrapping the neck with strong twine and applying a Palmer cervical clamp to prevent loss of blood from the head. The count of the head after this procedure was approximately the same as the count when the animal was alive. After a one-hour period to allow clotting of the blood, the skull was opened, the intracranial contents removed down to the level of the foramen magnum, and their volume determined by water displacement. A balloon was placed in the cranial vault, the bone replaced, and covered with the muscle and skin which had been reflected. The balloon was then filled with a volume of water equal to the volume of the intracranial contents, the head accurately repositioned in the head holder over the collimator and counted just as the living animal had been. This "phantom" was a mechanical approximation (from the standpoint of geometry, absorption, and scatter characteristics) of the living preparation. This count, originating from intravascular isotope in blood outside the intracranial contents and scatter from the body, contributes to the total count in the living animal. The limits within which this count might be assumed constant during the course of the experiment were investigated and will be discussed under the controls. The concentration of radioactive material in the cerebrospinal fluid was slight, being less than three-tenths of one per cent of the activity in the blood two hours after administration of the RIHSA. Five to ten microcuries RIHSA was then added to the water in the balloon and the head counted again (phantom plus RIHSA). An aliquot of the balloon contents was taken for counting in the well counter. This procedure provided the data for the establishment of a proportionality constant (k) between the scintillator used to count the head and the well counter.

Total blood volume was determined by a method in use by the radioisotope service of the Seattle Veterans Administration Hospital. Prior to injection, the RIHSA was loaded into a standard 2 ml. glass syringe. This syringe was then placed in a grooved wooden block to insure reproductible geometry and counted. This count will be referred to as "Block Count A." After injection the syringe was counted again (Block Count B). The difference between Block Count A and Block Count B is the count

injected as determined by this arrangement. The syringe was then washed into a one liter volumetric flask and the washing diluted to one liter with water. The syringe was then counted a third time (Block Count C). The difference between Block B and Block Count C is the count in the flask as determined by this arrangement. One ml. aliquots of the flask contents were counted in the well counter. The above data were then used to determine the count injected as determined by the well counter.

(1) counts injected as determined by the well counter equals

$$\frac{(\text{Block Ct. A} - \text{Block Ct. B})\ (\text{well count of 1 ml. of flask contents})\ (1000)}{(\text{Block Ct. B} - \text{Block Ct. C})}$$

To obtain blood volumes, 1 ml. blood samples were counted in the well counter after a 1/100 dilution. The total blood volume at the time a given sample was drawn could then be estimated as follows:

$$(2)\ \text{Total blood volume} = \frac{\text{counts injected as determined by the well counter}}{(\text{well count of diluted blood sample})\ (100)}$$

The following procedure was used to determine the percentage of blood in the intracranial contents from the scintillator counts from the living animal. The well count of the balloon contents (containing RIHSA) was determined. A proportionality constant (k) was then calculated to establish the relationship between counts obtained from the scintillator used to count the animal's head and the well counts added to each milliliter of the phantom.

$$(3)\ k = \frac{(\text{count phantom plus RIHSA}) - (\text{phantom count})}{\text{count/ml. balloon contents in well counter}}$$

The count from the intracranial contents of the living animal was taken as equal to the count of the living head less the count of the phantom, and (k) determined above was applied:

$$(4)\ k = \frac{(\text{head count, living animal}) - (\text{phantom count})}{\text{count/ml. intracranial contents in well counter}}$$

The percentage of blood in the intracranial contents during any minute was:

(5) Per cent blood in intracranial contents equals

$$\frac{(\text{count/ml. intracranial contents in well counter})\ (100)}{\text{count/ml. whole blood in well counter}}$$

Equations (4) and (5) each contain the term "count/ml. intracranial contents in well counter." Setting each equation equal to this term and then to each other and rearranging terms:

(6) Per cent blood in the intracranial contents equals

$$\frac{[(\text{head count, living animal}) - (\text{phantom count})]\ (100)}{k(\text{count/ml. whole blood in well counter})}$$

No additional corrections were made for scattering or absorption, as other workers[17] have shown scattering to compensate absorption at 3.5 cm. in a paraffin phantom, and this approximates the geometry of the preparation used in this study. Corrections were made for changes in plasma concentration of the isotope during the experiment.

The extraneous count arising from blood in tissues "seen" by the detector but outside the cranial vault, such as skin, muscle, and bone, has been treated as constant in the foregoing calculations. Control experiments were performed to determine the limits of this assumption. The thigh was placed across the collimator aperture and the body placed in the lead tunnel. With the same RIHSA dose used in the previous experiments, about the same counting rate was obtained from the thigh as had been obtained from the head. This count represented isotope in the blood of the tissues of the thigh. After a 30-minute control period, Diamox (150 mg. per kg.) was injected and the counts recorded as in the previous experiments. Using the mean phantom corrections and proportionality constants from the experiments in which the head had been counted, these data were treated as if they had come from the animal's head rather than the thigh. The extent to which this count varied during the course of the experiment was taken as the extent to which the extraneous count had

varied in experiments in which the head had been counted. This variation, taken as the limit of accuracy of the technic, was 0.8 per cent of the calculated intracranial blood volume.

An increase in blood volume was observed during the hour following administration of Diamox to the experimental animals. Control experiments were performed to determine the time course of this phenomenon. A short catheter was placed in the inferior vena cava through a femoral vein and a tracer dose of RIHSA was given, adjusted so that blood samples could be counted directly in the well counter without dilution. Serial blood samples were withdrawn to establish a control value, the usual dose of Diamox was administered, and blood samples taken over a one-hour period for blood volume and hematocrit determinations. Approximately 10 per cent of the blood volume was withdrawn during the course of the experiment.

RESULTS

Following Diamox injection there was an immediate rise in cerebrospinal fluid pressure and an associated increase in intracranial blood volume. The initial rise in pressure (peak at one minute) was followed by a fall and a second rise in cerebrospinal fluid pressure (peak at eight to ten minutes) which was associated with a decrease in intracranial blood volume to a level near the control value. Following the second cerebrospinal fluid pressure peak eight to ten minutes following injection, the pressure fell slowly to near normal levels in another 50 minutes. The intracranial blood volume rose from its depression associated with the second cerebrospinal fluid pressure peak and fluctuated about a level higher than the control value (figure 1). The same pattern of response was seen in all experiments.

One hundred microcuries of RIHSA gave counting rates of approximately 1,000 CPM from the head of an adult cat with the collimation and detection equipment used in these experiments. The over-all counting error was less than 10 per cent.

The hematocrit increased 10 per cent and the total blood volume increased approximately 15 per cent (corrected for the increased hematocrit and associated decrease in the isotope-containing plasma portion of whole blood). These changes, based on a single injection of RIHSA, reached a maximum within 20 minutes following Diamox administration and remained at their new levels throughout the one-hour period of observation. No significant change in blood volume was observed during the 30-minute control period prior to Diamox administration.[18]

DISCUSSION

These experiments were performed to test the hypothesis set forth in an earlier paper[3] that the cerebrospinal fluid pressure elevation produced by Diamox might be due to vasodilation and an increase in intracranial blood volume. The values of in vivo intracranial blood volume reported in this study agree well with the previously published values of 2 to 4 per cent for laboratory animals.[19,20]

The initial increase in cerebrospinal fluid pressure one minute following Diamox administration reflects an increase in arterial and venous pressures[3] and an increase in intracranial blood volume. The second cerebrospinal fluid pressure peak eight to ten minutes following Diamox is, however, associated with falling

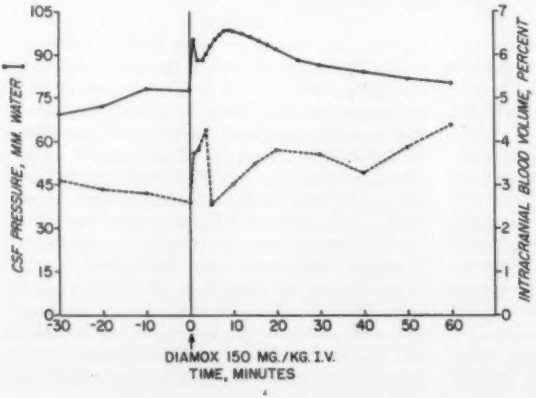

FIG. 1. Mean values of four experiments. The numerical ordinate for cerebrospinal fluid pressure (solid line) is on the left, and that for the intracranial blood volume (broken line) is on the right.

arterial and venous pressures[3] and an intracranial blood volume near the control level. This second pressure peak is thus not the direct result of increased intracranial blood volume. Either blood, brain, or cerebrospinal fluid must expand to produce the increase in pressure observed following Diamox administration. The intracranial blood volume is decreased during the most marked increase in cerebrospinal fluid pressure. Tschirgi[1] and Kister[2] have reported a decrease in the rate of cerebrospinal fluid production following the administration of Diamox, but in both studies the data were obtained from cerebrospinal fluid systems operating against atmospheric pressure rather than an appreciable hydrostatic pressure. This feature of their experimental designs makes extrapolation of the data to closed systems difficult. If the rate of cerebrospinal fluid reabsorption is decreased more than the rate of production, there would still be a net increase in intracranial pressure due to increased cerebrospinal fluid volume. If Diamox does decrease the rate of cerebrospinal fluid formation in the intact animal and if the rate of absorption is not altered by Diamox, the increase in intracranial pressure following Diamox administration in this study must reflect an increase in the volume of brain tissue per se. Since the volume of the erythrocytes, which are laden with carbonic anhydrase, increases following Diamox administration and since carbonic anhydrase is an important enzyme in adult brain tissue,[21] it might well be that Diamox produces an increased fluid uptake by brain tissue due to an increase in intracellular osmotically active carbon dioxide. The ability of basic substances to penetrate the blood-brain barrier[9] and the alkaline properties of Diamox (pK 9.1)[6] make entrance of Diamox into the brain probable.

It is thus clear that the initial rapid rise in cerebrospinal fluid pressure following Diamox passively reflects an increase in intracranial blood volume. However, the second rise in cerebrospinal fluid pressure cannot be explained on this basis, since the intracranial blood volume is reduced at this time. We feel that Diamox crosses the blood-brain barrier during the first few minutes. As intracellular carbonic anhydrase is inhibited, osmotically active carbon dioxide accumulates and cerebrospinal fluid pressure rises.

The observed acute increase in total blood volume can partially be explained on the basis of the increased hematocrit. Presumably the increase in red cell mass is also due to inhibition of the intracellular carbonic anhydrase with retention of osmotically active carbon dioxide.

The clinical utilization of parenteral Diamox in syndromes associated with increased intracranial pressure would thus seem to be contraindicated. Not only would this drug be presumably ineffective in lowering cerebrospinal fluid pressure under these circumstances, but the acute increases in pressure during the first hour might be deleterious.

SUMMARY

1. A method is described for the in vivo determination of intracranial blood volume.

2. In adult cats, intravenous Diamox (150 mg. per kg.) produced a bimodal increase in cerebrospinal fluid pressure, one peak occurring one minute following administration, and the other peak occurring eight to ten minutes following administration.

3. The first pressure peak is associated with an increase in arterial and venous pressures and an increased intracranial blood volume.

4. The second pressure peak is associated with falling arterial and venous pressures and an intracranial blood volume near the control values.

5. An increase in total blood volume, as determined by a RIHSA dilution technic, was observed reaching a maximum 20 minutes following Diamox administration and remaining elevated for another 40 minutes.

6. A 10 per cent increase in hematocrit was observed, following approximately the same time course as the total blood volume.

7. Parenteral Diamox would thus appear to be ineffective and potentially dangerous in the presence of increased cerebrospinal fluid pressure.

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■ The experiments of Professor Claude Bernard, Dr. Brown-Séquard, and others upon the cervical sympathetic, prove that when this nerve is paralyzed by dividing it, a state of hyperaemia, of which the most conspicuous signs are a bloodshot state of the conjunctiva and of the lining membrane of the nostril and ear, with a contracted pupil, and with increased temperature, is at once set up on the same side of the head: and also that when the end of the divided nerve which is separated from the cord is irritated, the immediate result is dilatation of the pupil, with an almost complete blanching and cooling of the parts which were bloodshot and warm a moment before. The vessels in these parts evidently relax and receive more blood when their nerves are paralyzed, and contract and receive less blood where their nerves are irritated; and the increased temperature and sensibility which happens in the one case, and the diminished temperature and sensibility which happens in the other case, are nothing more than the natural consequences of the increased or diminished quantity of blood in the parts in each case respectively.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Craniopharyngiomas in the Aged

Pascal Tiberin, M.D., Gil M. Goldberg, M.D. and Armin Schwartz, M.D.

IT IS GENERALLY RECOGNIZED that craniopharyngiomas, although primarily encountered in children and young adults, may become symptomatic at any period of life. Although the clinical features are quite characteristic in young patients, the mode of onset and symptomatology in the aged may be variable and confusing, making diagnosis difficult.

In this paper, clinical and pathologic data on two cases of craniopharyngioma in elderly people are reported, calling attention to the fact that this congenital tumor may remain silent until old age.

CASE REPORTS

Case 1. A 60 year old woman was admitted to the hospital on October 4, 1956 with a history of marked personality changes. For six months previously she had felt well, except for a progressive deterioration in vision, which had never been good, and that was attributed to hypertension. At that time she complained of headache, vague abdominal and limb pains, and general weakness. She gradually lost interest in her usual work, became sleepy and disoriented, developed urinary incontinence, and neglected her personal hygiene. One month prior to admission the patient became virtually blind.

On admission the patient was confused and her speech was almost incomprehensible. The skin was dry, slightly edematous, and wrinkled around the mouth. The axillary hair was absent and the pubic hair very scanty. Except for an enlarged liver, the systemic examination was negative. Blood pressure was 120/80. The neurologic findings were as follows: Bilateral primary optic atrophy with complete amaurosis. Both pupils were dilated and did not react to light. There were bilateral forced grasping and generalized hyperactive reflexes, as well as extensor toe sign on the left side.

Laboratory findings. Urine examination showed slight albuminuria, pyuria, and normal excretion of 17-ketosteroids. Blood cell count suggested normochromic anemia. Blood sugar was 74 mg. per cent, urea 28 mg. per cent. There was a pathologic response to an ACTH test. Erythrocyte sedimentation rate was 23/63. A chest film was normal. Roentgenograms of the skull revealed enlargement of the sella turcica, with decalcification and erosion of its dorsum and floor. Electroencephalogram was normal. Lumbar puncture showed clear colorless fluid with an initial pressure of 220 mm. of water. Protein content of the cerebrospinal fluid was 67 mg. per cent. Right percutaneous carotid angiography revealed narrowing and upward displacement of the anterior cerebral artery, with no filling of its supracallosal portion. Pneumoencephalography showed moderate symetric dilatation of the ventricular system.

On the basis of these findings, a diagnosis of pituitary adenoma was made. The patient was given cortisone and ACTH for two days prior to surgery and on the morning of the operation. On October 24, 1956 the chiasmal region was explored through a right transfrontal craniotomy. Elevation of the frontal lobe disclosed a tumor mass which proved to be partially cystic.

On aspiration 10 cc. of a clear light-yellow fluid was obtained, and the optic nerves could be visualized only after collapse of the capsule. The solid portion of the tumor was seen to protrude from the pituitary fossa between the stretched optic nerves into the region of the third ventricle. As it was impossible to remove all of the tumor without compromising the already damaged neighboring structures, the opening in the capsule was enlarged and soft avascular tissue removed for histologic verification only.

At the end of the operation the left pupil reacted sluggishly to light. In the immediate postoperative period the blood pressure and pulse were not obtainable. A Neosynephrine infusion was set up to maintain a minimal blood pressure of 100 mm. Hg. This was continued, together with cortisone (50 mg. daily), for 11 days. Although there was slight improvement in the first few days, she deteriorated steadily and died on the twenty-second postoperative day.

Autopsy was performed two hours after death. When the brain was removed, it was found that a tumor mass occupied the place of the pituitary gland and compressed the optic chiasm (figure 1). The tumor mass measured 5 by 4 by 3 cm. It was located partially intrasellar, but mostly extrasellar. The tumor was well delimited and no invasion into surrounding tissues was demonstrated. On sagittal section of the tumor, many minute cyst-like formations surrounded by grey-white soft tissue with areas of brown discoloration were found. Microscopic examination revealed the tumor to consist mainly of continuous sheets of squamous cells forming nests without cornification (figure 2). In other areas cystic formations with cylindrical pseudostratified epithelium lining were observed. No signs of malignant changes were

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observed. However, there were areas of necrosis, minute calcifications (figure 3), foreign body giant cells, and macrophages with hemosiderin pigment. On the rim of the tumor, a thin compressed normal hypophysial parenchyma was distinguished. *Pathologic diagnosis*: Craniopharyngioma.

Case 2. A 65 year old housewife was admitted to the hospital on February 24, 1955 because of a typical organic mental syndrome of nine months' duration. Past history and family history were not significant. About two years previously she had lost consciousness for a short period of time, but from then on and for a full year she was active and ran her house well. For nine months prior to admission she complained of headache, a feeling of pressure on the eyes and pain in the legs, with unsteadiness in walking and general weakness. During the same period her family noticed a considerable change in her behavior: she became apathetic and forgetful, slow in her speech and in the performance of simple routine tasks, slept much during the day, and was sometimes confused. In July 1954 she was seen in the outpatient department, but aside from retinal signs of arteriosclerosis she showed no neurologic signs. An electroencephalogram revealed low frequency waves, mostly at the rate of 4 c/s, occasionally intermingled with delta waves or short runs of delta waves in the anterior lower frontal regions as well as in the left temporal region. At that time an impaired cerebral circulation secondary to generalized arteriosclerosis was considered, and the patient underwent symptomatic treatment. Early in January 1955 she suddenly fainted for about five minutes and from then on her general condition became progressively worse; her family noticed that she drank a lot of water, and the patient became incontinent and neglected her personal hygiene.

On admission she was confused, disoriented as to time and place, and did not cooperate. The systemic examination was negative. Body temperature was 36.5° C., average pulse 60 per minute, and blood pressure 150/90. Owing to the lack of cooperation, the visual fields could not be obtained. Pronounced arteriosclerotic changes were present in both fundi. Except for an Oppenheim sign on the right side, there were no other neurologic abnoralities. During her stay in the hospital her general condition deteriorated further, the pulse rate was as low as 44 per minute, the blood pressure dropped to 90/60, and the body temperature to 35.2° C.

Roentgenograms of the skull, thorax, and abdomen were normal. Marked glycosuria was found. The fasting blood sugar was 435 mg. per cent, cholesterol 305 mg. per cent, and the erythrocyte sedimentation rate 66/105.

Repeated electroencephalograms revealed deterioration of the original findings and suggested an active deep-seated midline process, extending to the left. The possibility of hydrocephalus was considered, as well. Lumbar puncture showed a clear colorless fluid under normal pressure, containing 62 mg. per cent protein. Pneumoencephalography revealed considerable distention of the lateral ventricles, with a filling defect in the anterior part of the otherwise normal-sized third ventricle. The aqueduct and fourth ventricle were normal. These findings raised the suspicion of a space-occupying lesion in the anterior part of the third ventricle and, therefore, the patient was prepared for operation.

In March 1955, five weeks after admission, a right transfrontal craniotomy was performed by a transventricular approach, and a cystic mass was found to bulge into the lateral ventricle through the enlarged foramen of Monro. About 20 cc. of dark oily fluid was aspirated and a defect in the cyst wall was made for ventricular drainage.

The postoperative course was very stormy. The patient went into coma, a left hemiparesis developed, and she died on the ninth postoperative day.

Autopsy was performed about two hours after death. Only relevant intracranial findings will be noted. The region of the infundibulum was occupied by a tumor mass measuring 2 by 1.5 by 1.2 cm. The tumor consisted of a hard yellowish-grey parenchyma encircling a cyst. Microscopic examination showed that the cyst wall was formed by a pseudostratified epithelium and areas of squamous epithelial lining. Also observed were nest cells with necrosis, foreign body giant cells, and macrophages loaded with hemosiderin pigment granules (figure 4). The content of the cyst consisted of cholesterol and amorphic deposits. *Pathologic diagnosis*: Cystic craniopharyngioma.

DISCUSSION

Only a few observations of craniopharyngiomas in the aged have been reported. Witt and co-workers,[1] in reviewing the literature on incidence in patients more than 60 years of age, were able to find only five such instances among 454 cases assembled from ten different series. No clinical features were mentioned. They added two cases of their own, whose presenting symptoms related to visual disturbances. Of 86 intracranial tumors in the aged, Pennybacker[2] found three craniopharyngiomas in patients over age 60. Williams and Pennybacker[3] reported the case of a patient aged 63 with a history of progressive failure of memory and falling attacks, occasionally associated with loss of consciousness. Another case in an adult as old as 68 was only briefly mentioned by Davidoff and Feiring.[4]

In our patients the presence of mental deterioration formed the outstanding clinical manifestation and obscured the other less striking features. Whether psychic changes are due to local pressure on such structures as the third ventricle and frontal or temporal lobes or to the increased intracranial pressure secon-

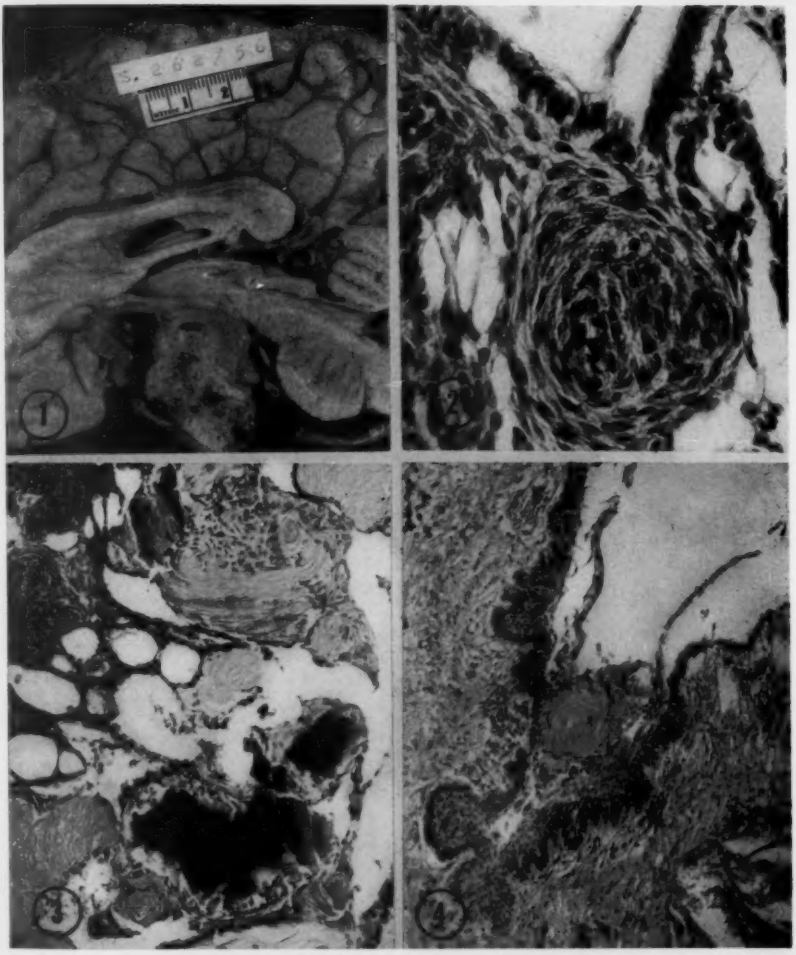

FIG. 1. *Case 1.* Tumor mass occupying the place of the pituitary gland and compressing the optic chiasms. Sagittal section demonstrating a well delimited tumor. Multiple cystic formations are visible.

FIG. 2. *Case 1.* Sheets of squamous cells forming nests without cornifications. A pseudostratified epithelial cyst is visible. Hematoxylin-eosin stain.

FIG. 3. *Case 1.* Cystic formation with epithelial lining, areas of necrosis, and calcifications. Hematoxylin-eosin stain.

FIG. 4. *Case 2.* Wall of a cyst formed by squamous cell epithelium. Necrotic nest cells are visible. Hematoxylin-eosin stain.

dary to hydrocephalus is still a matter of controversy. White and Cobb[5] reviewed the literature with regard to "psychological changes" in cases of giant pituitary neoplasms and craniopharyngioma. These authors stated that the presence of mental deterioration usually indicates suprasellar extension of the tumor and involvement of adjacent structures which may be of prognostic significance.

Except for the mental symptomatology evident in our patients, the clinical details were completely different in each case. Progressive failure of vision, as well as signs of pituitary and hypothalamic dysfunction and enlarge-

ment of the sella turcica, are findings common in any intrasellar space-occupying lesion with extrasellar extension. On the basis of the aforementioned findings, a preoperative diagnosis of pituitary adenoma was considered in case 1 because it is the most common lesion of this area in old people. The associated frontal lobe symptomatology in this patient (grasping, hyperactive reflexes and pyramidal signs) may have been due to interference with the blood supply, as demonstrated by angiogram. As no signs of increased intracranial pressure were found (in spite of proved hydrocephalus), in this case it is probable that the bradycardia and the relative hypothermia and hypotension were due to direct involvement of the hypothalamus. The loss of consciousness that marked the onset of the disease in case 2 is another feature worthy of mention. Penfield and Jasper[6] observed similar attacks in two of their cases. In one instance, the attacks were characterized by falling without loss of consciousness and in the other by simple loss of consciousness. In the absence of objective findings, the psychic signs evident in our second patient were explained before her hospitalization on the basis of cerebral arteriosclerosis (as suggested by the retinal picture). After air study was performed, a third ventricle tumor was diagnosed incorrectly. The difficulty in the differential diagnosis between brain tumors and cerebral arteriosclerosis has often been discussed.[7-9] The postoperative shock in case 1, as well as the final outcome in both, indicates that patients with hypothalamic lesions and failure of the pituitary gland are in no condition to respond to the stress of an intracranial operation.

SUMMARY

Two cases of craniopharyngioma in patients aged 60 and 65 are reported.

A comparison of these cases with those from the available literature suggests that there is no pathognomonic clinical picture of craniopharyngioma in the aged.

Mental deterioration may be the only manifestation and should lead to further investigation.

Suprasellar calcifications have not been demonstrated roentgenographically, in spite of their microscopic evidence.

In the absence of other objective findings the electroencephalogram may have considerable localizing value.

It is suggested that the condition is not as rare in advanced age as the paucity of reports would suggest, for apparently many such cases are unreported or escape detection because of their misleading symptomatology.

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Neurologic Manifestations of Thrombotic Thrombocytopenic Purpura

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NUMEROUS individual case reports and reviews[1,2] on thrombotic thrombocytopenic purpura adequately describing the clinical manifestations and pathologic findings have appeared in recent years. Nevertheless, thrombotic thrombocytopenic purpura is a rare disease, since only about 100 cases have been reported. Therefore, it is relatively unfamiliar to many neurologists. Since patients with this disease are often seen by the neurologist, either initially or in consultation, because of the prominence of neurologic manifestations, we have considered it advisable to review a series of 11 cases examined at the Columbia-Presbyterian Medical Center.

Moschowitz[3] in 1925 first described the pathologic findings in one case which manifested many of the clinical findings that are now associated with this illness. He termed it "an acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries." With the addition of other cases to the literature, there has been an evolution of a rather typical clinical picture and a better understanding of the pathologic features. There would seem to be three underlying processes in the disease: 1) thrombosis of small blood vessels, 2) hemolytic anemia, and 3) thrombocytopenic purpura. In any one case the symptoms and signs are produced by a combination of all three processes, any one of which may be more in evidence than the others.

The basic lesion is the occlusion of numerous arteries, arterioles, and capillaries by an amorphous hyaline material. Venules may be affected occasionally. The involved vessels may be located in any or all organs and tissues, but the heart, kidney, and brain are the most heavily affected. The nature of the thrombotic matter has not yet been ascertained. Most of the early investigators considered it to be composed of agglutinated platelets because of the similarity of the staining properties of the hyaline material and platelets.[4] More recent workers, however, have raised the question whether the thromboses may not occur secondary to a primary lesion in the walls of the involved vessels. Gore[5] has described changes in the walls of the vessels beneath the epithelium, consisting of a collection of hyaline material which is thought later to protrude into the vessel lumen where platelets accumulate on its surface. Endothelial proliferation may then recover the surface of the hyaline mass. Orbison[6] noted dilatation of the occluded portions of the small arterioles, with the development of minute aneurysms. By the use of reconstructed serial sections he has shown that these aneurysms occur at the arteriolar-capillary junction. The endothelial proliferation associated with this syndrome frequently occurs in the area of the occlusion but may also be found unassociated with a thrombus. This also suggests the likelihood of an initial vascular lesion.

Hemolytic anemia, the second feature of the syndrome, is at times severe and is probably due to the action of an extracorpuscular hemolytic mechanism.[7] Transfused corpuscles from normal donors are rapidly destroyed. Reticulocytes and other immature red cell forms appear in the blood and spherocytes are often seen. An increase in the mechanical and osmotic fragility of the cells has been found,[7,8] but the Coombs test indicating the presence of globulin antibodies has usually been negative.[1,7,9] In response to the anemia, erythroid hyperplasia of the bone marrow is a usual finding.

Thrombocytopenia is the third feature of the malady. The platelet count is frequently in the range of 20,000 to 40,000 per cu. mm. and the bleeding time is prolonged. The fate of the lost platelets is not known, but it has been postulated that their incorporation in the arteriolar thrombi may be the cause of their depletion.[4] It is more likely, however, that the thrombocytopenia is due to the presence of an as yet unidentified platelet autoagglutinin[10] and/or to decreased production of platlets.[11]

Singer[2] reported that the disease occurs with equal frequency in males and females. It has been found in both Negroes and whites. Patients from nine and one-half to 69 years of age have been affected. Singer divided the

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disease into an acute and chronic form but was able to find only two cases in the literature which fitted into the later classification.[12,13]

The disease is frequently said to have its onset following a mild respiratory infection, although the relationship of this to the illness is not known. The first complaints are often vague but they are occasionally directly related to the central nervous system. Headache, generalized weakness, anorexia, nausea, vomiting, dizziness, abdominal pain, arthralgias, and blurred vision were noted in the present series. Following this, alteration in mentation, aphasia, convulsions, and weakness of the extremities have been noted, as well as pallor, hematuria, purpura, and jaundice. Lethargy follows and the patient soon lapses into coma and expires. The illness usually lasts from a few days to several months, although a relapsing course of as long as three years has been reported.[12,13]

CASE PRESENTATIONS

A brief summary of five previously unreported cases will serve to point out the main clinical and pathologic features of the disease.

Case 7. A 47 year old white female secretary was admitted to the Neurological Institute on June 14, 1954 with a complaint of generalized headaches for two weeks. Otherwise she had been well until three or four days before admission when she developed bilateral numbness of the face and began to have episodes of twisting of the mouth, thick speech, and weakness of various extremities. On the day of admission she was unable to speak or write for a period of time. No history of allergy or drug ingestion was elicited.

On admission the patient was drowsy, confused, and uncooperative, with temperature 101.0°, pulse 100, and blood pressure 120/70. There were ecchymoses over the upper and lower extremities. On neurologic examination the reflexes on the left were more active than on the right, although no abnormal reflexes were noted. The remainder of the examination was normal.

Laboratory findings. The hemoglobin was 4.2 gm. per 100 ml.; erythrocytes 1,900,000 per cu. mm; leukocytes 9,000 per cu. mm., with 85 per cent neutrophils, 10 per cent lymphocytes, 4 per cent myelocytes, and 1 per cent eosinophils. Anisocytosis, poikilocytosis, macrocytosis, and polychromasia were found in stained smears. A few nucleated red cells were also seen. The platelets numbered 35,000 per cu. mm. Reticulocyte count was 14 per cent. On examination of the urine, there was 1+ albumin, 3+ glucose, and a moderate number of white blood cells. Bilirubin content of the blood was 0.9 mg. per 100 ml. Sedimentation rate was 30 mm. per hour. A lupus erythematosus preparation was negative, as was the direct Coombs test. Prothrombin time was 14 seconds (normal 14 seconds). On osmotic fragility testing hemolysis began at 0.44 per cent and was complete at 0.28 per cent (normal 0.42 to 0.30 per cent). Clotting time was seven minutes. The bone marrow showed marked erythroid hyperplasia. The cerebrospinal fluid was not examined.

Course. The patient became disoriented and required the use of restraints. On June 22 she was noted to have a right hemiparesis, with bilateral Babinski signs. There was facial grimacing and marked salivation. On July 22 she lapsed into coma and remained in this state until her death on August 4. The course was febrile, with the temperature reaching 105.0° terminally. For the first nine days following admission she was treated with cortisone 300 mg. once a day and with ACTH 40 mg. once a day for the next three days. Four transfusions of 500 ml. each were also administered. None of the therapy had any apparent effect. Postmortem examination was not performed.

Although an autopsy was not obtained in this case, the clinical and laboratory findings would seem to point quite clearly to the diagnosis of thrombotic thrombocytonic purpura. The hemolytic anemia, thrombocytopenia, and prominence of neurologic signs are typical of this syndrome. Hereditary, idiopathic, and symptomatic hemolytic anemias as well as drug reaction seem to be ruled out by the negative family history, the absence of drug ingestion, the negative Coombs test, and the severity of neurologic involvement. The possibility of lupus erythematosus or periarteritis nodosa presenting with a predominantly hematologic picture remains. Again the type of neurologic manifestations, the negative L.E. test, and lack of other signs or symptoms of these two collagen diseases would militate against their presence. Therefore, the diagnosis would seem to be thrombotic thrombocytopenic purpura.

Case 8. A 45 year old Negro truck driver was admitted to Presbyterian Hospital on April 12, 1955 because of disorientation for 12 hours. One week before admission he developed anorexia, nausea, and vomiting. These symptoms were present intermittently until the time of entry. Hematuria was noted for the four days preceding admission. On the morning of admission the patient became incoherent and restless. The past history is significant in that the patient had been addicted to heroin, for which he was treated in 1953 at the United States Public Health Center in Lexington, Kentucky. Following discharge he became addicted to morphine and at the time of admission was taking 120 mg. of morphine intravenously every day.

On examination the patient was well developed but dehydrated. The sclerae were icteric. Temperature was 102.0°, pulse 88, and blood pressure 150/60. The skin over the arms, abdomen, thighs, and buttocks was covered with crater-like scars from infected needle puncture sites. A fresh puncture wound was present on the volar surface of

the left forearm. A gallop rhythm was present. On neurologic examination he was disoriented, inattentive, and restless. His speech was incoherent. The left pupil was larger than the right but reactive. The remainder of the examination was unremarkable.

Laboratory findings. The hemoglobin was 8.5 gm. per 100 ml.; erythrocytes 2,250,000 per cu. mm.; leukocytes 12,000 per cu. mm., with 76 per cent neutrophils, 21 per cent lymphocytes, and 3 per cent monocytes. There was anocystosis and sickling of the red cells. The platelets numbered 24,000 per cu. mm. A sickle-cell preparation was negative. Reticulocyte count was 17 per cent. There was 2+ albumin, 1+ glucose, 50 red cells, and an occasional white cell in the urine. Sedimentation rate was 25 mm. per hour. Fasting blood sugar was 159 mg. per 100 ml. and bilirubin was 4.6 mg. per 100 ml. Thymol turbidity and cephalin flocculation were both negative. Prothrombin time was 13 seconds. Bleeding time was nine minutes. Direct Coombs test was negative. Blood cultures were negative. Bone marrow showed erythroid hyperplasia. The cerebrospinal fluid was under a pressure of 110 mm. of water. It contained one lymphocyte and a protein of 54 mg. per 100 ml. Serologic test for syphilis was negative, as was the lupus erythematosus preparation. There was mild diffuse slowing without clearcut focal signs in the electroencephalogram.

Course. During the first three days of hospitalization the patient remained restless and disoriented, requiring large doses of sedation. On the morning of the third day he was found to be alert, cooperative, and oriented. His memory was poor, however, and he was unable to calculate. There was ataxia in the upper and lower extremities on the right. The patient remained in good condition throughout the day, but in the evening he had a generalized seizure followed by coma. During the coma there was rigidity of all extremities with hyperactive reflexes in the lower extremities and bilateral Babinski signs. The patient expired on April 16, about eight hours after the seizure, with a temperature of 106.0°. An autopsy was performed.

Case 9. A 32 year old Puerto Rican housewife was admitted to Presbyterian Hospital on August 14, 1955 because of joint pains for one week. She had been well until August 8, when she developed a sore throat, anorexia, arthalgias, and ankle edema which persisted until admission. On the day prior to entry her vision became blurred and she developed a mild frontal headache. The patient was in the sixth month of an uneventful pregnancy and had had one previously normal pregnancy 11 years before. In 1947 she had an appendectomy and removal of an ovarian tumor and in 1949 an exploration of the right kidney, both in another hospital.

On admission she was pale and lethargic with a temperature of 99.8°, pulse 88, and blood pressure 160/100. There was a loud harsh precordial systolic murmur. Liver and spleen were not palpable. Photophobia and blepharospasm were present. There was decreased sensitivity to pain over the first and second divisions of the right trigeminal nerve, and a right homonymous hemianopia was present. The remainder of the examination was unremarkable.

Laboratory findings. The hemoglobin was 8.7 gm. per 100 ml.; erythrocytes 2,400,000 per cu. mm.; leukocytes 12,000 per cu. mm., with 69 per cent neutrophils, 30 per cent lymphocytes, and 1 per cent monocytes. There was hypochromia, macrocytosis, and polychromasia in the stained smears of the blood. There were 15 nucleated red cells per 100 white cells. The platelets numbered 32,000 per cu. mm. Reticulocyte count was 12 per cent. The urine contained 2+ albumin, many red cells, and 15 white cells per high-power field. Bilirubin was 0.5 mg. per 100 ml. A lupus erythematous preparation was negative. Direct and indirect Coombs tests were negative and no saline or albumin agglutinins were present. Prothrombin time was 14 seconds. Bleeding time was one minute and 15 seconds. Blood cultures were negative. Bone marrow showed mild erythroid hyperplasia. The cerebrospinal fluid was under a pressure of 140 ml. and a Kolmer test on the fluid was negative. The gamma globulin was 18 per cent (normal below 13 per cent). An electroencephalogram was abnormal because of slowing and poor organization.

Course. On the day following admission the patient delivered a still-born macerated fetus. Shortly after this she lost all vision and lapsed into coma. Petechiae were noted over the trunk and extremities. Terminally her reflexes became hyperactive and there were bilateral Babinski signs. Several hours before death she had a number of transient episodes of extensor rigidity. Two blood transfusions of 500 ml. each did not alter the course of the illness and she died on August 19, 1955. An autopsy was performed.

Case 10. A 60 year old Negro housewife was admitted to Presbyterian Hospital on September 17, 1955. The patient had apparently been well until the week before admission when she began to complain of nausea, vomiting, blurred vision, and bilateral frontal headaches. She also had several episodes of confusion. For seven years the patient had had hypertension, with pressures ranging as high as 220/120. For this condition she had taken various unidentified antihypertensive drugs.

On examination the patient was lethargic and confused. Temperature was 99.4°, pulse 84, and blood pressure 144/80. Arteriosclerotic retinopathy was present. There was an apical presystolic murmur and an aortic systolic murmur. The first mitral sound was loud. The liver was questionably enlarged and the spleen tip was palpable. The patient demonstrated an organic mental syndrome characterized by perseveration and an inability to follow two-stage commands. The remainder of the examination was normal.

Table 1

SUMMARY OF CLINICAL DATA IN ELEVEN CASES OF THROMBOTIC THROMBOCYTOPENIC PURPURA

(Diagnosis proved by autopsy in all except case 7)

NO.	AGE SEX RACE	LENGTH OF ILLNESS	SYMPTOMS*	GENERAL EXAMINATION	NEUROLOGIC EXAMINATION	COURSE IN HOSPITAL	SEIZURES	SPINAL FLUID
1.	21 MW	9 mos.	Headache, anemia 6 mos. Albuminuria 5 yrs.	T 98.6°, chronically ill, bleeding gums, petechiae, hepatomegaly.	Delirium, hyperactive reflexes.	Progression to coma with death in third month.	No	Not examined
2.	44 MW	3 wks.	Headache 3 yrs. Tinnitus and deafness rt. ear and epigastric distress 3 wks. Transient weakness rt. upper extremity and aphasia 1 day. Confusion 8 hrs.	T 100.5°, icteric, pale, sub-conjunctival hemorrhages.	Uncooperative, confused, aphasic, slight right facial paresis, slight ataxia of gait.	Developed petechiae, generalized seizures, coma, and high fever. Died on twelfth day.	Yes	4 WBC, Protein 46
3.	32 FW	6 days	Progressive generalized weakness, epigastric pain, vomiting, and disorientation 6 days.	T 101.6°, icteric, pale, ecchymoses, petechiae, bleeding gums, hepatomegaly.	Drowsy, restless, and disoriented.	Transient episode of shock followed by loss of consciousness. Death on day of admission.	No	Not examined
4.	16 FW	2 mos.	Headaches, blurred vision, diplopia 10 days. Left hemiparesis 1 day.	T 98.6°, normal examination.	Drowsy, indifferent, left hemiparesis, large right pupil.	Improvement of hemiparesis. Following onset of seizures lapsed into coma. Died in eighth hospital week.	Yes	2 WBC, Protein 35
5.	40 FW	3 mos.	Headache, weakness, confusion, nominal aphasia, nausea, increasing drowsiness 2 mos.	T 101.4°, acutely ill, slightly icteric, petechiae on soft palate.	Indistinct optic disk margins, retinal hemorrhages, confused.	Gradual depression of consciousness to coma. Death on 27th hospital day.	No	Not examined
6.	37 FW	21 mos.	Headache, dizziness, diplopia 20 mos. Hypertension 2 mos. Generalized seizures, confusion, restlessness, disorientation, right upper quandrant pain 3-4 days.	T 102.4°, BP 210/140, petechiae, ecchymoses, mild cardiac failure, bloody urethral discharge.	Confused, restless, disoriented, generalized weakness, bilateral Babinski signs, papilledema, rightfixed pupil.	Rapid progression to death on third hospital day.	Yes	Protein 62
7.	47 FW	2 mos.	Headaches 2 wks. Bilateral numbness of face, seizures of varying focal motor and sensory origin 4 days. Expressive aphasia 1 day.	T 101.0°, ecchymoses over extremities.	Uncooperative, with left reflex preponderance.	Became disoriented with right hemiparesis and bilateral Babinski signs, lapsing into coma. Death in sixth week. Cortisone 300 mg. o.d. was given for 9 days and ACTH 40 mg. o.d. for 3 days.	Yes	Not examined
8.	46 MN	11 mos.	Nausea, vomiting, epigastric pain, weakness 1 wk. Hematuria 4 days. Disorientation 12 hrs.	T 100.0°, dehydrated and icteric.	Restless, disoriented, inattentive, speech incoherent, large left pupil.	Mentation returned to normal. Then had seizure and developed decerebrate state. Died on fourth hospital day.	Yes	Slight xanthochromia, 1WBC, protein 54
9.	32 FW	12 days	Sore throat, ankle edema, arthralgias, anorexia 1 wk. Blurred vision, headaches 1 day.	T 99.4°, BP 160/100, pale, lethargic, systolic murmur, petechiae, 6 mos. pregnancy.	Photophobia, right homonymous hemianopia, hypalgesia right upper face.	Had still birth, lost all vision, and lapsed into coma. Died on fifth hospital day.	Terminal decerebrate episodes.	1 WBC, protein 31, gamma globulin 18%
10.	60 FN	15 days	Blurred vision, headache, nausea, vomiting, and confusion 1 wk.	T 102.0°, lethargic.	Lethargic, acute organic mental syndrome.	Lapsed into coma, and developed generalized seizures. Died on eighth hospital day. Hydrocortisone 200 mg. o.d. was given 4 days before death.	Yes	Slight xanthochromia, 46 RBC, protein 64
11.	31 FN	15 days	Urinary urgency and frequency 1 wk., back pain 2 days.	T 98.6°, costovertebral angle tenderness, 8 month pregnancy.	Normal on admission	Had still birth, developed aphasia and delirium and lapsed into coma. Died on eighth hospital day. Hydrocortisone 100 mg. o.d. was given for 2 days and then prednisone 240 mg. o.d. for 5 days before death.	No	Not examined

*In general order of appearance.

Laboratory findings. The hemoglobin was 6.9 gm. per 100 ml., erythrocytes 2,100,000 per cu. mm., and leukocytes 14,150 per cu. mm., with 78 per cent neutrophils, 13 per cent lymphocytes, 3 per cent eosinophils, 3 per cent monocytes, and 3 per cent premyelocytes. There was anisocytosis, polychromasia, spherocytosis, and sickling of the red blood cells. There were four nucleated red cells per 100 white cells. The platelets numbered 29,000 per cu. mm. Reticulocyte count was 14 per cent. The urine contained 4+ albumin, 1+ glucose, 8 red cells, 2 white cells, and casts in each high-power field. Sedimentation rate was 65 mm. per hour. Cephalin flocculation and thymod turbidity tests were negative. Blood urea nitrogen was 62 mg. per 100 ml. Prothrombin time was 14 seconds. Both the direct Coombs test and a lupus erythematosus preparation were negative. Mechanical fragility was 8.8 per cent (normal 1.0 to 5.0 per cent). On osmotic fragility testing, hemolysis began at 0.675 per cent and was complete at 0.325 per cent. Blood cultures were negative. The cerebrospinal fluid was under a pressure of 200 mm. of water. The fluid was slightly xanthochromic and contained 46 red cells per cu. mm. The protein content was 64 mg. per 100 ml. and the serology test was anticomplementary.

Course. There was a steady progression of the organic mental syndrome, with eventual lapse into coma and death on September 25. While in coma she had several left-sided seizures. Purpura was never noted. During the four days prior to her death she was treated with hydrocortisone 200 mg. once a day without alteration in the course of her illness. An autopsy was performed.

Case 11. A 31 year old Negro housewife was admitted to Presbyterian Hospital on December 28, 1956 because of urinary urgency and frequency for one week. She was in the ninth month of an uneventful pregnancy, with an expected confinement date of January 23, 1957. This was her first pregnancy. During the two days before admission she had developed recurrent low back pain, facial puffiness, and bleeding from the gums and lips. On routine prenatal examination in November 1956 a positive Kolmer test and a positive treponemal immobilization test were obtained. The patient was given 14.4 million units of penicillin in 2 per cent aluminum monostearate over a five-week period.

On examination the patient was alert and well nourished with temperature 98.6°, pulse 86, respirations 20, and blood pressure 110/70. Tenderness was present in the left costovertebral angle. Uterine contractions were felt, but no fetal heart beat was heard. The remainder of the examination was unremarkable.

Laboratory findings. The hemoglobin was 5.9 gm. per 100 ml.; erythrocytes 1,920,000 per cu. mm.; leukocytes 7,950 per cu. mm., with 71 per cent neutrophils, 21 per cent lymphocytes, 1 per cent myelocytes, 1 per cent eosinophils, and 6 per cent monocytes. Anisocytosis, poikilocytosis, macrocytosis, and spherocytosis were found on stained smears. Six nucleated red cells per 100 red cells were seen. The platelets numbered 36,000 per cu. mm. A sickle-cell preparation was negative. Reticulocyte count was 2.2 per cent. There were many red cells and a 2+ albumin in the urine. Bilirubin was 1.1 mg. per 100 ml. Both the thymol turbidity and cephalin flocculation tests were negative. Prothrombin time was 12 seconds. The direct and indirect Coombs tests were negative. There were no saline or albumin agglutinins present. Two lupus erythematosus preparations were negative. Several stools were tarry and contained blood. The bone marrow showed erythroid hyperplasia.

Course. On the day following admission the patient delivered a still-born macerated fetus. During the next several days subconjunctival hemorrhages developed and lethargy appeared. On the sixth day of hospitaliaztion she was found to be totally aphasic, with inability to speak or to follow commands. The left pupil was larger than the right but the remainder of the neurologic examination was unremarkable. On the next day she was more alert and the aphasia was less. She rapidly became unresponsive, lapsing into coma, and ecchymoses appeared. The entire course was febrile and her temperature was 101.6° shortly before death on January 5, 1957. Despite the administration of 11 blood transfusions of 500 cc. each, together with hydrocortisone 100 mg. once a day for two days and then prednisone 240 mg. once a day for five days, there was no alteration in the course of the illness. Dilantin 0.4 gm. once a day had been given for the last five days of life. An autopsy was performed.

ANALYSIS OF CASES

Clinical Findings

The chief features of these five cases, in addition to those from six cases reported previously from this institution,[14] are outlined in table 1. The neurologic manifestations are summarized in table 2.

The ages of the patients ranged from 16 to 60 years, with eight of them between 30 and 50 years of age. Three of the patients were Negroes and the remaining eight white. Eight patients were female and two of these were pregnant at the onset of their illness. The entire length of the illness varied from six days to 21 months. Practically all patients had some symptoms referable to the central nervous system during the course of the illness and all eventually died in coma. Frequently it was the neurologic difficulty which first brought the patient to the hospital. In six of the ten cases the first complaint was headache, while another complained initially of blurred vision. One of the remarkable findings was

TABLE 2

NEUROLOGIC MANIFESTATIONS IN ELEVEN CASES OF THROMBOTIC THROMBOCYTOPENIC PURPURA

Number of Cases	*Signs and Symptoms*
10	Alteration in mentation (confused, restless, drowsy, hyperactive, inattentive, and disoriented)
6	Seizures (generalized in 5, focal in 1)
4	Aphasia
3	Blurred vision
3	Paresis (hemiplegia in 2, monoplegia in 1)
2	Papilledema

the alteration in mentation which was displayed by ten of the patients. This could best be classified as a delirium, for the patients were described as confused, restless, drowsy, hyperactive, inattentive, and disoriented. In all but two cases these alterations were progressive and preceded the development of coma. Case 11 had a slight transient improvement and case 8 reverted to an almost normal mental state but had a seizure and lapsed into coma. Aphasia was present in four cases.

Seizures were an outstanding feature of the illness and occurred in six patients. The seizures were all generalized with the exception of one (case 7) in which there were focal fits of varying motor and sensory origin. An additional patient had recurrent episodes of decerebrate rigidity terminally. Seizures were often a late sign; in three instances the convulsion heralded the onset of terminal coma.

Blurred vision was a complaint in three patients. One of these (case 9) had a right homonymous hemianopia when first examined. Over the next few days this progressed to total blindness. Her fundi were not abnormal and at necropsy the cortex showed severe involvement in both calcarine areas. Although the fundi in the other two patients were normal, the cause of the blurred vision was not investigated further. Papilledema was noted in two other patients and pupillary changes were seen in an additional three cases.

In spite of the plethora of central nervous system signs, there were only two patients who developed hemipareses and another had a slight facial weakness and transient weakness of an upper extremity. Alterations in the reflex pattern and the occurrence of an abnormal plantar response were not unusual. Case 9 had hypalgesia over the first and second divisions of the trigeminal nerve on the right. Although the symptoms in general were progressive, there were two notable exceptions. Cases 8 and 11 returned from delirium to an improved mental state and case 4 showed improvement of a hemiparesis.

Lumbar puncture was performed in six patients. The fluid was slightly xanthochromic in two instances but was never bloody. The cell counts were all within normal limits and the highest protein recorded was only 64 mg. per 100 ml. A gamma globulin determination was performed in one instance (case 9) and found to be 18 per cent (upper limit of normal is 12 per cent).

Electroencephalograms were taken on three patients and were diffusely abnormal in two, while case 4, who had a left hemiparesis, showed a slow-wave focus on the right.

In all cases there was evidence of a severe hemolytic anemia and thrombocytopenia. The direct Coombs test and the lupus erythematosus preparations were negative in six cases. Mechanical and osmotic fragility were increased in one instance, while the osmotic fragility was normal in another case. Case 10 had filter paper electrophoresis performed on the hemoglobin which was normal.

Cortisone, 300 mg. once a day, was used for nine days and ACTH, 40 mg. once a day, for three days to treat case 7 without benefit. Hydrocortisone, 200 mg. once a day, was administered to case 10 for four days prior to death without altering the course of the disease. Case 11 received hydrocortisone, 100 mg. once a day, for two days and then prednisone, 240 mg. once a day, for five days without improvement.

Pathologic Findings

Autopsies were performed in ten of the 11 cases. The postmortem findings in six of the cases have previously been reported by Vassar and Spain[14] and the results of the examination in the four remaining cases were not dissimilar. They will be summarized together in the following paragraphs.

Grossly there were few abnormalities seen. Splenomegaly and small hemorrhagic areas were common findings. Cardiac valvular vegetations were present in four cases. On microscopic examination the basic pathologic process characteristic of this syndrome was noted

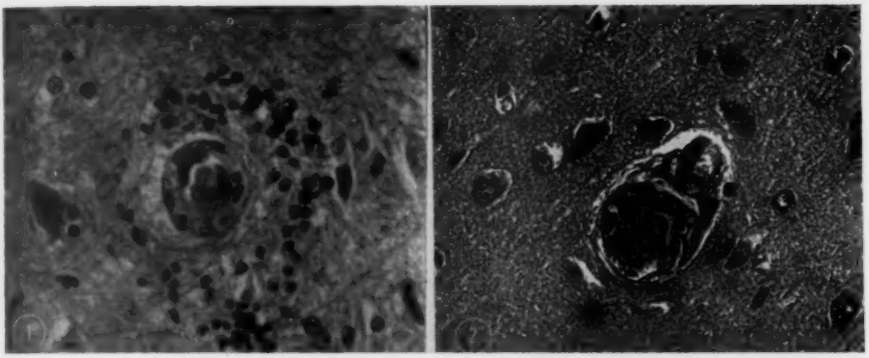

FIG. 1. Photomicrograph of an arteriole in the gray matter of the midbrain, showing endothelial hyperplasia without the presence of hyaline material. The vessel is still patent and surrounded by a small area of hemorrhage. Hematoxylin eosin stain.
FIG. 2. Photomicrograph of an arteriole in the gray matter of the cerebral cortex, showing both endothelial hyperplasia and the occluding hyaline thrombus. Hematoxylin eosin stain.

in all cases. This was composed of two features. One was the presence of the occluding masses of hyaline material in the small arteries, arterioles, capillaries, and occasionally venules. The other was the endothelial hyperplasia in the walls of both the occluded vessels and at times also those not containing the hyaline substance. Although many organs were implicated by these changes, the brain, heart, and kidneys were involved in every case examined. The thrombotic material was an amorphous eosinophilic staining substance, and the walls of the vessels containing this material were frequently dilated and thin walled. In many instances the thrombi showed evidence of organization, giving credence to the theory that the lesions may occur in showers and also giving a possible explanation to occasional fluctuation of signs and symptoms.

In the myocardium, thrombosis of the vessels was associated with necrosis and fibrosis of surrounding areas. Kidney lesions were mainly in the cortical areas and occasionally the glomerular tufts were affected. In most of the cases the remaining abdominal organs and the striated muscles were involved less frequently. The bone marrow was hyperplastic in all instances.

In six cases where examination of the central nervous system was performed, the typical vascular lesions were noted in all cases (figures 1 and 2). As has been observed by Adams and associates,[15] the vessels of the gray matter of the hemispheres and the brainstem were most involved. In three cases (cases 5, 9, 10) the vessels of the white matter were implicated in varying degrees. In these cases it was mainly the subcortical white matter adjacent to marked cortical involvement which was affected. In one patient (case 9) the lesions were severe enough to produce softening of the brain in the left occipital pole. The gray matter surrounding the thrombotic arterioles and capillaries demonstrated changes varying from ischemic necrosis of the ganglion cells with a loss in their number to areas of cystic degeneration. Some of the more acute lesions contained polymorphonuclear cells, while in some older lesions varying degrees of astrocytosis were noted. The finding of petechial hemorrhages in the acutely involved areas was not uncommon, and, in one instance, a small subarachnoid hemorrhage was observed. The petechial hemorrhages were limited to the gray matter in all instances. Thrombotic lesions in the white matter caused swelling and fragmentation of axons. The spinal cord was examined histologically in two cases and was normal.

It was difficult in most instances to correlate clinical findings with the pathologic changes. However, in case 9 the bilateral severely involved calcarine areas accounted for the patient's blindness. In general, the clinical picture of delirium, aphasia, seizures, and blurred vision can be explained by cortical lesions. Alterations in the state of consciousness are probably based on a combination of cortical and brainstem lesions.

DISCUSSION

Etiology

The etiology of thrombotic thrombocytopenic purpura is unknown. Because it was originally thought that the vascular lesions were similar

to those produced in the Shwartzman phenomenon,[16] an allergic etiology was hypothesized. On a number of points, however, there are differences between the two phenomena. Singer[2] remarked that the Shwartzman phenomenon takes place in venules with an initial hemorrhagic lesion. This is followed by leukocytic infiltration of the vessels and the platelets thrombose as a result of this inflammation.[17] This is unlike thrombotic thrombocytopenic purpura, in which Gore[5] has demonstrated an initial subendothelial change from which the thrombotic material appears to have its origin. Nevertheless the disease has been found in patients sensitive to various drugs, including the sulfonamides[18,19] and possibly iodine.[20] Symmers[21] reported a case associated with sensitivity to oxophenarsine which was accompanied by acute hemorrhagic leukoencephalitis. Recently there has been an attempt to relate the illness to the group of collagen diseases. Approximately five cases have now been described in which the thrombotic syndrome has been associated with the "wire loop" kidney changes and various other findings of lupus erythematosus.[22–24] A case of periarteritis nodosa with platelet thrombi has been reported by Symmers and Gillett.[25] In discussing the relationship between the platelet thrombosis syndrome and the collagen diseases, Beigelman[22] pointed out that lupus, periarteritis, and platelet thrombosis may each be a different response to the same type of reaction, depending on the portion of the vessel affected. Thus, if the perivascular mesenchyme is the shock organ, lupus results; if it is the vessel wall, periarteritis occurs; and when the intima is the region responding, the thrombotic syndrome results. This is an attractive but, of course, an unsubstantiated theory. There have also been cases of thrombotic thrombocytopenic purpura occurring in siblings of patients with lupus erythematosus[7,26] and periarteritis nodosa.[27] Lazlo and co-workers[24] pointed out that the vegetations of non-verrucous endocarditis found in some cases of thrombotic thrombocytopenic purpura are similar to those found in lupus. In further investigations of this illness, therefore, this possible relationship will continue to remain an important factor to be considered.

In addition to the two women in the present series who developed thrombotic thrombocytopenic purpura during pregnancy, Miner, Nutt, and Thomas[28] have also reported a case in which the condition occurred during pregnancy. Pritchard, Weisman, Ratnoff, and Vosburgh[29] studied three women who had thrombocytopenia, hemolytic anemia, and seizures in association with toxemia of pregnancy. One of the patients recovered and the histologic findings in the other two were consistent with either eclampsia or lupus erythematosus but not thrombotic thrombocytopenic purpura.

DIAGNOSIS

As has been noted above, the neurologic signs and symptoms of thrombotic thrombocytopenic purpura may be either the main manifestation of the illness, the first manifestation, or both. In every case studied the central nervous system showed some degree of involvement. Because of this, the neurologist will frequently be called upon for help in diagnosis and he should have some familiarity with the syndrome. When initially seen the patient is usually found to have both a hemolytic anemia and a thrombocytopenia combined with neurologic signs. The signs and symptoms of the central nervous system involvement are most often those of a diffuse lesion of the gray matter. The common findings therefore are seizures, aphasia, cortical blindness, and an organic mental syndrome. Alterations in the reflex pattern and severe pyramidal tract disturbances, such as a hemiparesis, may be seen. Although fluctuation of the neurologic signs is said to be usual, this was not a constant feature in the present series.

If the triad of hemolytic anemia, thrombocytopenia, and neurologic involvement is kept in mind, the diagnosis should not be difficult. There are only a few other diseases which must be considered in the differential diagnosis. The greatest difficulty will be encountered in distinguishing it from the symptomatic hemolytic anemias which are associated with malignancy, leukemia, Hodgkin's disease, lupus erythematosus, and periarteritis nodosa. Occasionally each of these may be accompanied by a marked thrombocytopenia and neurologic signs. In these diseases, however, the systemic manifestations as well as the results of laboratory tests should provide help in the diagnosis. In addition, the nervous system involvement in these illnesses is usually different from that observed in thrombotic thrombocytopenic purpura. A transient but similar clinical picture has been observed in association with bacteremia and blood should always be taken for culture.[30]

In Hodgkin's disease, carcinoma, and leukemia the neurologic manifestations are caused by direct invasion of the brain, the cord, or

their coverings by the disease process. In leukemia cerebral hemorrhages are seen occasionally. In periarteritis the usual neurologic finding is a peripheral neuritis, although involvement of the central nervous system can be seen rarely. Lupus erythematosus produces focal neurologic signs late in its course, but the other manifestations of the illness should serve to differentiate it from thrombotic thrombocytopenic purpura. In those instances where the diagnosis is not clear, biopsy examination with a demonstration of the characteristic histologic changes should settle the issue. Symmers[31] feels that a combined rib, muscle, and skin biopsy may be the method of choice. In cases 7, 8, 9, 10, and 11 the diagnosis of thrombotic thrombocytopenic purpura was made before death. In case 7, although no confirmatory histologic study was performed, the picture was considered typical enough to include the case in this series.

TREATMENT

Treatment has been almost uniformly unsatisfactory. Singer[12] has made an extensive review of therapy and has been able to make few recommendations. Anticoagulants have been used in an attempt to prevent the thrombi from developing, but these compounds may actually cause further bleeding in the presence of thrombocytopenia. Both platelet and blood transfusions are of value from a supportive standpoint, but the platelets are removed rapidly from the circulation and the cells are destroyed by the hemolytic mechanism. Anticonvulsant medication may be useful in preventing seizures which occur so frequently in this illness. ACTH and cortisone have been used because of their frequent beneficial effect in the hemolytic anemias[32] and their effect in raising depressed platelet counts and preventing ecchymoses.[33] The results of treatment with the hormones in thrombotic thrombocytopenic purpura are difficult to evaluate but they probably deserve the benefit of further trial in this uniformly fatal illness. Singer[2] concluded his discussion of the value of splenectomy with the statement that "The surgeon and the patient's relatives should be told that death may follow rapidly after operation but that there is a slight chance of inducing temporary improvement." Several authors have recently reported favorable results, however, in patients presenting with the triad of thrombotic thrombocytopenic purpura who were treated with hormones and splenectomy.[34,35]

SUMMARY

1. A review of 11 cases of thrombotic thrombocytopenic purpura points out the prominence of neurologic manifestations in this rare hematologic and vascular disease.

2. The illness has three basic constituents: vascular thrombosis, thrombocytopenia, and hemolytic anemia.

3. The neurologic signs and symptoms are produced by the thrombotic vascular lesions located, for the most part, in the gray matter of the cerebral hemispheres and brainstem.

4. Delirium, seizures, aphasia, cortical blindness, and coma are common findings.

5. Etiology of the syndrome is unknown but it may be related to the collagen diseases.

6. Therapy has been of little benefit, although adrenal cortical hormones and splenectomy are still under investigation.

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■ Palsy chiefly consists in the loss of the power of voluntary motion, for sensation in a greater or less degree generally remains; nay in certain cases it is morbidly increased. I have seen several instances in which paralytic persons have felt very violent pain in the parts affected, particularly in the shoulder and arm. These remarks might be confirmed by quotations from various authors. — I never saw a case of palsy in which sensation was entirely lost; and an eminent physician of great experience asserts that a total loss of feeling in this disease is extremely rare. The other senses are often but little injured; sometimes they remain wholly unimpaired, and several instances might be adduced in which they appeared to be preternaturally acute. Dr. Heberden attended a paralytic person, whose sense of smelling became so exquisite as to furnish perpetual occasions of disgust and uneasiness; and he mentions one case in which *all* the senses became exceedingly acute.

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

What We Need to Know About Muscle

H. Stanley Bennett, M.D., Albert Szent-Gyorgyi, M.D.
Dereck Denny-Brown, M.D. and Raymond D. Adams, M.D.
—Moderator: Augustus S. Rose, M.D.

MODERATOR: The research committee of the American Academy of Neurology welcomes you to the third Symposium of Inquiry. This annual evening meeting, which was begun as an effort to stimulate more widespread interest in research, has proved popular, and the large attendance tonight testifies to the importance of this year's subject and to the prominence of the panel of speakers. The topic is: "What We Need to Know about Muscle."

In opening this symposium, I call to your attention that the committee, in selecting muscle as the subject for presentation, recognized the magnitude of the task requested of our eminent speakers, and attained their participation with an understanding that only portions within their respective disciplines would be selected for discussion. We are privileged to have a most distinguished panel. Dr. H. Stanley Bennett will present morphology; Dr. Albert Szent-Györgyi, biochemistry; Dr. Derek Denny-Brown, physiology; and Dr. Raymond D. Adams, pathology.

Although diseases of muscle are not common, most of them are without well established cause and no satisfactory therapy has been determined. In one sense it is remarkable that a tissue of such bulk and of such highly differentiated function should be as free of defect and disorder as is muscle. It is also remarkable that, in spite of its size and importance, relatively little is known about normal muscle. Possibly an explanation for some of these considerations may be found in the absolute dependence of the organism on the effector organ and in the ontologic age of muscle. Contractility is almost synonymous with life itself. The first speaker is Dr. Bennett, professor of anatomy at the University of Washington, Seattle.

DR. H. STANLEY BENNETT: It would appear that the American Academy of Neurology, in enlisting the participation of members of this panel, confronted them with a difficult challenge. I feel prompted to protest that, in science, one can see dimly only a short distance into the unknown, and I doubt if we are really in a strong position for formulating very definitive concepts about "what we need to know." But in broad terms, I believe one can point out the framework upon which an understanding of muscle structure, muscle function, and muscle disease must ultimately be supported. This is the framework of quantum mechanics.

The labors of many minds have brought us to the view that in muscle contraction important interactions occur between proteins, such as actin and myosin, and smaller compounds, such as adenosine triphosphate or creatine phosphate. Here we may remind ourselves that precise structural studies of simple compounds, such as the hydrogen, water, and benzene molecules, have been of decisive importance in permitting the formulation of an understanding of the intramolecular bonding forces operative in the molecules and of their interactions with neighboring chemical configurations. So also an understanding of the detailed molecular and electronic anatomy of ATP, of creatine phosphate, or of choline phosphate can be expected to yield concepts essential for satisfactory correlation of form and function at the molecular and electronic levels.

Thus, we may ask, what is there about the molecular structure of the nucleotide which makes this strange triad of heterocyclic base, pentose, and phosphate so important in physi-

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ology? What is there about the anatomic disposition of electron orbitals in these trinitarian compounds? What is there about the behavior of their electrons, in excited and in ground states, which endows nucleotides in so many variant forms with such important places on the honor roll of metabolic governors, messengers, and participants? What are the important common features of electronic anatomy and behavior shared by all mono-, di-, and polynucleotides which render this family of compounds effective in so many different ways and in so many different guises?

We may likewise profit our counsel by addressing our queries toward a related but not identical structural and physiologic problem—one related to phosphate esters. Through the brilliant exercises of Lippmann and others, we have learned to think of some phosphate ester linkages as "energy rich" and hence of special physiologic importance, whereas other phosphate ester groups yield less heat on hydrolysis and command less attention. If there exist these two different types of phosphate ester linkages with such different energetic properties, then it follows that these two groups of phosphate compounds should differ anatomically at the molecular level. That is, each group should differ from the other with respect to such important electronic parameters as bond distances, bond angles, electron orbital distribution, and the like. When appropriate studies of the molecular anatomy of such compounds have been consummated—and such studies are feasible and can be based on roentgenographic diffraction and on spectroscopic approaches—when we come to understand the molecular morphology of these compounds, we can expect at the same moment to gain considerable insight into their physiologic behavior. In all these examples the correlations of form and function at the electronic level will be in terms of quantum mechanics.

In asking that you now focus your attention on the structure of muscle as it can be envisioned at the macromolecular level, I will use an illustration taken from the important 1946 paper of Hall, Jakus, and Schmitt. I use this in honor of their pioneering successes in opening the field of muscle morphology to reasonable interpretation in terms of modern protein chemistry. I can summarize much by saying that evidence from two different lines leads us to take the view that myosin appears to be characteristically localized in the *A* bands, though it may be absent or modified in the *H* and *M* regions. Actin seems to be present in *I* and in *A* bands, but absent from *H* and *M*. We have no good evidence relating to the chemical nature of the *Z* band, though it is definitely not a membrane but has a fibrous character.

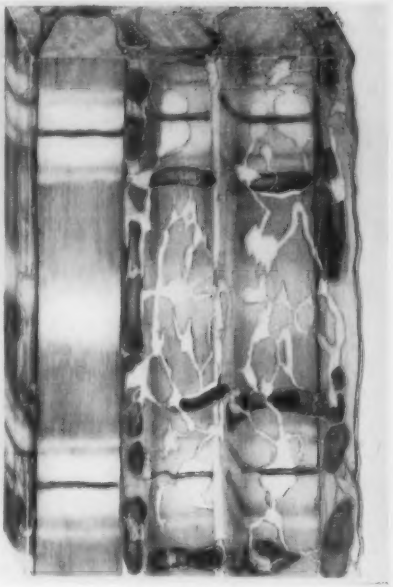

FIG. 1. A schematic representation of a block of striated muscle showing relations of myofibrils, sarcoplasmatic reticulum, mitochondria, and sarcolemma. The sarcolemma is represented on the right. The elements of the sarcoplasmatic reticulum are attached to the sarcolemma at the levels of Z bands and entwine around myofibrils, entering into a special relation with the myofibrils at the Z band level. Mitochondria, with their internal cristae, are disposed in the sarcoplasm.

The chemical characterization of *H* and *M* bands is also undetermined. We have no satisfactory evidence on which to base concepts of localization and arrangement of tropomyosin, myoglobin, or of any structural muscle protein other than actin and myosin, nor have we good basis for localizing within the muscle important nucleotides such as ATP.

But one can say something about the organization of myofilaments within the myofibril. Recently I have been persuaded to espouse the model of the sarcomere proposed by Hugh Huxley (1957), whose design I have set before you. This model conceives of two interdigitating sets of myofilaments which, on cross section, constitute a two-fold hexagonal pattern.

One set of filaments, which are thin ones and which, Huxley holds, contain actin, are anchored in the *Z* band and extend in each direction through the *A* band as far as the *H*, on the border of which they terminate. A second set of filaments, thicker ones containing myosin, are thought to interdigitate with the thin myofilaments in the *A* band and to be connected across the *H* and *M* continuously into the adjacent *A* of the same sarcomere. In contraction, Huxley postulates an interaction between components of thick and thin filaments which sets up interfilamentary bonding forces characteristic of the contraction phase. These forces are thought to exert traction on the thick filaments so that their free ends are caused to approach the next *Z* band, while the thin filaments deepen their penetration toward the center of the sarcomere. Professor H. H. Weber has proposed in a tentative and exploratory way a series of specific chemical reactions which, he believes, might involve side chains adorning members of each type of filament and which might result in contractile forces of the type envisioned by Huxley. It may well be that we are in a position to formulate the biochemistry of muscle contraction within this anatomic framework. Although the early evidence for Huxley's model was not very convincing, he recently completed a study, now in press (1957), which brings forth very impressive evidence in support of his model. Such is the power and persuasion of these new micrographs of Huxley's that I believe his model will come to dominate the literature of the next few years, and may well come to form the basis for concepts of muscle structure of lasting value.

I wish now to turn your attention to another feature of muscle morphology—one which has enjoyed little flattering attention from physiologists and biochemists but which demands, I believe, detailed study by all who are interested in muscle function. Over half a century ago, Veratti (1902), a pupil of Golgi, demonstrated with great elegance and beauty a reticular structure in the sarcoplasm of striated muscle fibers from a variety of vertebrates and invertebrates. Veratti's light microscope studies established the grosser topography of the sarcoplasmatic reticulum and depicted its main features and most common variants. His plates provide the best existing illustrative material on which to base an introductory understanding. The gross features of the reticulum may vary somewhat from muscle to muscle. In a few instances, the reticulum forms a random irregular three-dimensional network enmeshing the myofibrils, as in the muscle of an embryo mouse. But such irregular configurations are exceptional and, as a rule, the reticulum shows a considerable degree of order. This order can be related to the cross bands of the sarcomere. In such ordered cases, transverse members are constantly present, stretching all the way across the muscle fiber, forming in cross section a series of meshes embracing individual myofibrils. These transverse members may lie at the level of the *M* band in some muscles, or in other variants, at the level of the *Z*, or at the junction of *A* and *I* bands. In many types of muscle longitudinal strands of reticulum are also found. In some cases, the longitudinal connections may be so disposed as to connect only pairs of transverse meshes straddling an *M* band or a *Z* band. In other variants, longitudinal strands may connect all transverse mesh planes. The reticulum sends out members which establish contact with the sarcolemma at the outer border of the fiber. This contact with certain portions of the excitable plasma membrane of muscle may well provide an important key to understanding the function of the reticulum. In muscles with bizarre or unusual arrangements of the myofibrils, as shown in the cross sections of muscles actuating the dorsal fins of the seahorse or the flight muscles of a fly, the transverse meshes of the reticulum are adapted to the geometric peculiarities of the myofibrils. Where tracheoles pipe gaseous oxygen intracellularly right into the muscle fiber, as they do in some insect muscles, the reticulum may show structural adaptations related to the intracellular tracheoles. At certain preferential locations—frequently at the level of the *Z* band—the reticulum appears to establish some special kind of contact with the myofibrils.

Very recently, Porter and Palade (1957) have completed a detailed electron microscope study of the submicroscopic structure of the sarcoplasmatic reticulum. Although their paper is still in press, they have kindly consented to permit me to discuss their work and to show their slides. They have found that the reticulum conforms in distribution to the patterns shown by Veratti. They have found that it consists of a series of interconnected vesicles and channels enclosed by membranes, forming a system of flattened tubes adorned at certain places with bulbous enlargements. In one variant, the reticulum shows a continuous transverse series of braided channels embracing

each myofibril at the level of the *M* band, and sending tubular branches ending in cistern-like enlargements at the level of the Z bands. Here the bulbous terminal comes into close apposition to its fellow pertaining to the next sarcomere, and between the two large members Porter and Palade have discovered some special smaller vesicle-like structures. These show at high magnification as rows of tiny double margins of the terminal enlargements of the reticulum strands. It is clear that we are here seeing details of the special connections between reticulum and Z bands recognized by Veratti. In cross section the small intercisternal vesicles appear to be elongated and to penetrate appreciably into the myofibril between the surface myofilaments. In other types of muscles, as in mammalian cardiac muscle, similar connections between reticulum and myofibrils have been discovered at the level of the junction of *A* and *I* bands, rather than at the Z. Porter and Palade have also found special connections between the reticulum and sarcolemma, as illustrated previously by Veratti. The excitable sarcolemma may be indented deeply at the level of the Z. Near the recesses of this crypt the reticulum comes into close relation with the sarcolemma. A number of vesicles may adorn the vicinity. I end by offering a diagram of my own (figure 1) which represents functional contact between reticulum and myofibril at the level of the Z. The reticulum is also shown as engaging the sarcolemma at the right of the picture. Here one is reminded of the suggestion of Retzius, proffered in 1881, and repeated by Veratti in 1902, that the sarcoplasmatic reticulum might serve as an internal transverse conducting structure in muscle. One can conceive of a propagated excitation moving along the sarcolemma and activating transverse members of the reticulum at points where the reticulum touches the sarcolemma. From these pick-up spots the impulse can be envisioned as traversing the membranes of the reticulum across the fiber transversely, gaining access to myofibrils deep in the fiber in rapid succession through the specialized connections here depicted at the Z. Andrew Huxley and Taylor (1955) have recently demonstrated that localized transverse conducting members do exist in muscle. The sarcoplasmatic reticulum is the only structure to which one can reasonably attribute this function. Surely this interesting structural feature of muscle is worthy of competing for at least part of the attention which physiologists and biochemists now lavish on the contractile portion.

Thus we have glanced at some of the current concepts of muscle anatomy, from which we can send exploratory feelers forward in search for more of what we need to know about muscle.

MODERATOR: Biochemistry of muscle will be presented by Dr. Albert Szent-Györgyi, director of the Institute of Muscle Research, Woods Hole, Massachusetts.

DR. ALBERT SZENT-GYÖRGYI: I am in a very bad spot because I am given fifteen minutes and asked to talk about what I don't know, and there is so much that I don't know. If I would have to say what I know, I would have it off in five minutes.

There is one general remark I would like to make before starting: There is no such thing as "the muscle." "The muscle" has misled many people. Muscle is an organ to make motion; there are many sorts of motion and thus there are many sorts of muscle. For instance, for A. V. Hill the frog sartorius is *the* muscle. The frog's sartorius is just a muscle which helps the frog jump. The frog has to sit and wait for the fly to come. It has to jump to catch the fly at the intercept of the two curves, that of the fly and of his jump. There are very few of us who make our living in this way! So there are enormous differences between muscle and muscle, which have to generate a very certain type of motion on which life may depend. There are slow muscles, tonic muscles, quick muscles, all sorts of muscles, but fortunately there are also common basic features. I have always emphasized in my writings that there are no real differences between cabbages and kings, and that there are many common things between any two live tissues; so there are common things between muscles, too, and I would like to talk on these.

My first slide (figure 1) shows you a muscle fiber as you see it through the light microscope (rabbit's musculus psoas, monochromatic light). This instrument, the microscope, we use very little today. It went out of fashion with two other instruments, namely brains and eyes, which yielded their place to electronic hardware. The muscle fiber in figure 1 has a membrane which you don't see. This may be good because we don't know anyway what the membrane is. We call "membrane" something which is there, which nobody has really seen yet and which does something when excitation shoots along. We know it is there because

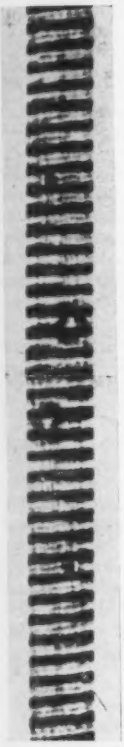

FIG. 1. *(left)* Fiber from the musculus psoas major of the rabbit. Rest length. Glycerol extracted. Total length 0.09 mm. (photo by B. Horvath).

FIG. 2. *(right)* Longitudinal section of a muscle fibril from the thoracal (wing) muscles of the housefly. EM. The two dark lines at the end are Z lines.

there is an electric potential between the inside and outside of the fiber which collapses in excitation. A ring of depolarization runs all along the membrane and elicits the contraction inside. Now whatever else happens that you can see, as for instance, contraction, is always the result of the action of smaller fibrillar units. This slide (figure 2) is a very masterly electron microscopic picture. It is an insect muscle which shows you that muscle fiber is composed of a great number of still much thinner fibers. This is a masterly section because the fibers are only 120 to 150 angitrons thick and, as you see, the whole section is just one sheet of fibers. They are actomyosin fibers. They are composed of two proteins: myosin, discovered a hundred years ago by Kühne, and actin, discovered in my laboratory some 20 years ago. These two are made to contract by the adenosine triphosphate molecule which exists in muscle in large quantities. We can make threads out of actomyosin and can make these threads contract with ATP. It was one of the most exciting moments in my life to see this mysterious motion happening *in vitro*. We produced this motion first by adding muscle juice to the fiber. Then we identified the substance which elicits the contraction as ATP. ATP does two things: It elicits the contraction and at the same time it supplies the energy for it. The energy is in the P-O-P bond, which has about ten thousand calories. The history of ATP is very colorful. We discovered that it elicits contraction and supplies the energy. Then, three or four

years ago it was discovered that it is not ATP at all which does all this, but lately ATP is beginning to do it again. The energy content also varied. It went down from twelve thousand calories to four. Lately it is rising again.

The sum of this whole story is that the ATP makes the actomyosin go into a state of contraction and loses its P-O-P bond. The muscle does external work, and the ATP pays for it with its P-O-P bond. In muscle, evidently, the low-energy state is the contracted state. When the muscle does external work, it loses its own energy. The resting muscle can stay in the relaxed state because there is no actomyosin in it. There are actin filaments and myosin filaments side by side, but at a distance at which they could not interact. They are kept apart by electrical repulsive forces which are just in balance and just in excess of the attractive forces. When the excitation comes along the membrane, this balance is upset and actin mixes with myosin. We don't have the least idea what mediates between the membrane and actomyosin. But anyway the balance gets upset and actin and myosin get together and as soon as they are together in the presence of ATP they have to contract and go over into the low-energy contracted state, since all physical systems always tend to go to the lower level of energy. All of this is very important for clinical considerations of physiologic function of muscle, and that is why I am wasting my time on it. What brings actin and myosin together are electrical attractions of charged points. These charges are balanced by ions. The negative carboxylic groups are balanced by potassium ions. The positive groups are balanced by negative ions. This explains why the function must depend to a very great extent on the potassium concentration, or, more exactly, on the concentration of potassium plus sodium. Actomyosin is a very stupid substance: it doesn't know the difference between sodium and potassium. Only the membrane is intelligent enough. What happens if we get a little more potassium into the muscle than is needed? A ten per cent change in the potassium and sodium concentration makes all the difference between zero contraction and maximal contracture. Increase the potassium and sodium concentration by five per cent and the muscle will not contract at all whatever we do to it and will have no force. If you decrease it five per cent, it will go into contracture. So all those states of muscle where you have contracture may all be due to a defective balance of ions or, more exactly, due to defective function of the cell membrane which somehow lost its ability to keep the ionic balance in order.

These balances will have a special importance in the heart muscle. In a classic experiment a century ago, Bowditch showed that, instead of working better, it worked less after he stopped the heart. We have studied this phenomenon by allowing less and less frequency to the heart. With a decrease of frequency the force of the beat decreased. We could show that in rest the fiber gains sodium and potassium, just a little too much. There are substances in serum which enable the membrane to keep the ions out so that with a change of frequency, there is no change of force. All of these things are of great importance for clinical study. The striated body muscle has a very good membrane and such changes do not occur very easily, but in the heart the situation is more subtle and there is more danger of an accumulation of ions. We could also show that death may be due to a slight accumulation of potassium ions. I have no patients myself except frogs and goats, but I could show that the heart of a frog (which died because his heart stopped) can be brought back to life again by slightly decreasing its potassium ion concentration. With this decreased potassium you wouldn't know the difference between the heart which was a dead one and a perfectly healthy one.

Let us have a look again at the whole muscle. How does the whole muscle work? Where does the energy of ATP come from? It comes from bread and butter. It is like in the subway: you can't put a button in the automat—you must put a dime in. So in muscle you must put in ATP; nothing else will make it contract. Now where is the bread and butter transformed into ATP energy? This is in the mitochondria. The more the muscle has to work the more mitochondria there are.

Now, to sum up the whole function of the muscle: First we have the resting muscle fiber. Then comes excitation, which finds a very good membrane with 100 MV potential at the nerve ending. This potential is depolarized at one point and then the depolarization shoots along the membrane, whereupon the actomyosin contracts. Now you would ask what connects membrane and actomyosin? Nobody knows. I conceived a very beautiful theory, which I think is the right one. With Dr. Bay, we have shown that when the depolarization rushes along there is a powerful longitudinal electrical field set up inside the

muscle, and there is also a somewhat weaker cross field set up which has been overlooked until now. Nobody has really calculated it or thought it could trigger the contraction. We have calculated it and it has most remarkable mathematical properties, just the ones which you would expect from something that triggers off muscle. I still think that this electric field is one of the most important factors in muscle physiology. I can illustrate how divergent the ideas in this field are by telling you that when we wrote our paper we sent it to *Science* and I got the manuscript back saying that this is not new, Helmholtz knew it all. Then I sent the paper to the journal *Neurology*. They sent it back saying that it was so new they don't dare to print it. Then I sent it to the *Journal of Physiology* and they sent it back asking whether it was a joke or a paper? So we published it in Chicago in a mathematical paper and since then, in England, Knudson has shown that all of our experiments were wrong. However, lately a very fine worker here in America, Dr. A. Csapo, has shown that all of Knudson's experiments were wrong, and probably it is really this electric field (we call it the window field) which triggers off muscle.

I have spent all my time and now I shall say a few general, almost philosophic words. As I told you, we know very little about muscle. I told you actomyosin makes contraction. You would ask now what does actomyosin really do when it shortens? We have worked on the problem for 20 years and have no answer. A. Huxley and Weber produced a theory lately, but I find it difficult to accept. It is beautiful work, but you can interpret it different ways. We know a very great deal about the chemistry of myosin, but we don't know what contraction is. We don't have the least idea of how actomyosin goes over into the shortened state. But this lack of knowledge is not limited to muscle. If you think for a moment about the whole of biology and biochemistry, you will find something very peculiar: the coexistence of highlights with utter darkness. We do not understand the most basic and simple problems. I have worked 20 years with actomyosin and I know it contracts with ATP, but I don't know what contraction is. We have all the wonderful hormones in hand. We can write down their formulae, but if you ask what is a hormone really doing, there is no answer! Of happenings on the molecular level, we don't have the slightest idea. You know the latest work on proteins, but what is a protein for? Why did nature build it? No answer. As long as we have chemical substances and reactions which we can explain in terms of classic chemistry, we are most successful. As soon as we come to motion, to actions, such as those of hormones, we have not the least idea, and the reason is probably that some very, very important factors are still missing from our knowledge. I think I have discovered three of them. One is electronic excitation in the triplet state, the second is water, and the third the electromagnetic field. I am emphasizing this because I feel the trend in present thinking that, if there is a problem, then one can hire a scientist and say: here is a problem and you solve it. Here are the books of biochemistry. You mix up their contents and out comes the answer. There is so much to be learned yet about the foundations of nature! We have a very poor knowledge about the really basic facts and that is why we are so badly stuck in solving pathologic problems. It is said that cancer keeps more people alive than it kills, and it will keep people alive for a very long time to come if we don't try to get down to the bottom of nature.

MODERATOR: Dr. Derek Denny-Brown, James Jackson Putnam Professor of neurology at Harvard Medical School and Boston City Hospital, will discuss muscle physiology.

DR. DEREK DENNY-BROWN: After Dr. Szent-Györgyi's graphic description of the physical properties of muscle proteins, I would like to discuss some differences between muscles that may be more important in pathology than was formerly thought. For example, muscles vary in color and it is natural to look for differences in function that correlate with such color differences. In the rabbit these color differences are quite remarkable, the soleus, crureus, and semitendinosus muscles being brick red and the other muscles of the leg being pale and colorless. The same differences are present, though less obvious in cat, monkey, and man. The red muscles contract more slowly than the pale, the twitch of soleus being about three times the duration of that of gastrocnemius in the cat, about two times in man. The red muscles are more constantly occupied in postural reflexes, but only relatively so. The pale muscles are more exclusively employed in the gallop, hop, and leap response in animals. The pectoral muscles of birds that soar in flight are red, whereas those of the wing flapping domestic hen are pale. Yet slowness in contraction is not necessarily associated with red color, for in the pigeon the twitch of the red pectoral muscle was

found by us to be of the same duration as that of a pale leg muscle in the same bird. Contrariwise the twitch duration of extraocular muscles in the cat is found to be only one-sixth that of a pale leg muscle in the same animal, yet the color of these two is approximately the same. The color of the muscle fiber is dependent on its content of myoglobin and this is in turn only indirectly related to speed of contraction. Is it possible that both these are related to liability to fatigue? Merton has shown that fatigue is directly related to the degree to which strong contraction causes ischemia by impeding capillary circulation. In the rabbit pale muscles fatigue in response to a tetanic stimulus somewhat more easily than red muscles, but in the cat there is no significant difference.

Myoglobin is finely dispersed in the sarcoplasm and is not demonstrable by the light microscope. It is of interest that Vaughan and Pace have shown it is increased much more than is hemoglobin by continuous exposure to high altitude, presumably to maintain an optimum oxygen gradient between the cell membrane and the cytochrome in the mitochondria.

For many years histologists confused redness, or content in myoglobin, with a darkness in muscle fiber in cross section. This darkness affects all the fibers in most red muscles, but only some in pale non-pigmented muscles, producing a patchy appearance. The darkness is due to the presence of lipid granules in the sarcoplasm which are responsible for the longitudinal striation. Such granules disappear in emaciated states, both from red and pale muscles, and are greatly increased by adiposity, though the twitch duration and the redness do not alter. Ability to store lipids, then, is an independent function possessed by most fibers in red slow muscles and in varying degree by fibers of fast pale muscles. Some of the muscle fibers in any muscles are unable to store fat, in even the most adipose animal. Red muscle fibers are usually larger in diameter in mammals, but this largeness appears mostly due to the greater fat content. Content in glycogen is another variable that is unrelated to redness or speed of contraction. All types of fiber become smaller in starvation, but this loss of diameter also does not affect twitch duration or redness. Clinicians are often surprised by the strength and tenacity of muscular contraction of very thin emaciated people.

We showed many years ago that all muscles in the newborn kitten are granular and slow in contraction, and that during the first six weeks of life the pale muscles become paler, develop freedom from lipid in most fibers, and shorten greatly in speed of contraction. The red muscles develop their redness later. Therefore, we feel that these differences are all aspects of special differentiation of function. Of particular interest was the incidental finding that in the pectoralis muscle of the pigeon, where the pale fibers are very large and the dark fibers very small, both could be innervated by the same nerve fiber, indicating that the process of differentiation was not primarily related to innervation or even the pattern of innervation. In general, however, slower muscles and small dark muscle fibers are innervated by smaller nerve fibers.

These histologic aspects of muscle function have again assumed importance in the last four years, since Kuffler and Gerard have clearly demonstrated that there are two types of muscle fiber in many frog muscles in terms of neuromuscular transmission. This finding has revived an earlier controversy following Kultchitsky's demonstration in the 1920's that in frog and lizard there were two types of motor nerve endings, one innervated by a nonmedullated fiber plexus, lying epilemmal, and another by more conventional medullated fiber and motor plate, thought to lie under the sarcolemma. Hunter and others postulated a tonic function for the first and a phasic contractile function for the second. The nonmedullated fibers always innervated small dark fibers, the medullated layer pale, lipid-free fibers. We now know that both endings are epilemmal and both are derived from somatic motor nerve roots. In the adult mammal such anatomic difference has not been found. The only adult mammalian structures in any way comparable are the small intrafusal muscle fibers of the muscle spindles, which are innervated by much smaller nerve fibers than the remainder of the muscle, with medullation to near the termination.

The arrival of a nerve impulse at a motor nerve ending sets up a small end plate potential, which in normal mammalian muscle immediately sets up a membrane action potential that rapidly spreads along the length of the muscle fiber detonating contraction of the myofibril contents as it travels. Stimulation of the myofibrils by an electrode introduced into the fiber contents causes only a localized contraction of a few segments of the related myofibrils. Only exceptionally does such a locally induced contraction spread slowly along the

myofibrils and, if so, there is no action potential. Conversely, if the muscle fiber is completely fatigued, the membrane action potential may spread the length of the fiber but not induce contraction. The end plate potential is clearly due to the release of acetylcholine which, by altering the permeability of the muscle membrane under the motor ending, causes a localized depolarization that sets up the spreading depolarization underlying the action potential. Curare, by blocking the depolarization produced by acetylcholine, or an electrotonic depolarizing current which opposes such depolarization, blocks the formation of an action potential and leaves only the small end plate potential (e.p.p.) following arrival of each nerve impulse. Decamethonium or a steady hyperpolarizing electrotonic current applied locally opposes depolarization of the region of the end plate and so blocks the setting up of an action potential in another way.

The peculiarity of the very slow fiber system in frog muscle demonstrated by Kuffler and Gerard and subsequently worked out by Kuffler is that its electric potential seems to correspond to only the end plate potential of faster muscle fibers. Several potentials seem to be necessary to set up a contraction. There are many endings along one muscle fiber, as if the transmitting property of the muscle membrane is poorly developed. Once set up, such a contraction is associated with a prolonged positive after-potential pointing to a slow restitution of polarization, associated with prolonged contraction of the myofibrils. The slow muscle fiber is also more sensitive to acetylcholine than the faster fibers and to depolarizing electrotonic currents, and in these respects resembles muscle fibers that are undergoing atrophy as a result of denervation, and also the reactions of fetal muscle fibers. These reactions of the slow muscle fibers found scattered in some muscles of amphibia explain the peculiarly slow "tonic" pharmacologic effects in the form of delayed relaxation, called "contracture," that figured so prominently in early studies of the frog nerve-muscle preparation. You may remember from physiology that such reactions in the frog are seasonal, the winter frog being liable to greater contracture. They also bring vertebrate muscle into perspective in relation to crustacean muscle, which has a remarkable ability to summate end plate potentials. Slow muscle fibers of this type are very sensitive to the effect of Veratrin and other drugs producing effects resembling myotonia.

Up to this point, the differences I have outlined have been characterized as sharp distinctions into red and pale, dark and clear, slow and fast, tonic and phasic types of muscle fiber, according to the histologic, mechanical, or electrical criteria employed. It has been natural to seek two different types of muscular function corresponding to these differences. I have already pointed out that these and other differences may vary independently, so that there must be more than one type of specialization. There is now additional evidence that this is so and that in all striated muscle there are relative differences in the same muscle. In the past I have presented evidence for a uniform speed of contractile process in all the fibers in any mammalian muscle, but it now seems possible that there is some variation from fiber to fiber in the larger muscles that is not detected by any present recording method. The contractile characteristics of the muscle fiber are not rigidly fixed. Kruger has pointed to the primitive arrangement of the myofibrils in the slow muscle fibers studied by Kuffler in frog muscle, which clearly resembles the early arrangement of myofibrils shown by Haidenhain in the developing trout. In the frog the proportion of these fibers and the corresponding degree of "tonic" response lessen as winter passes into summer. The non-medullated innervation of such fibers (Kultchitsky) only reflects failure of myelin to extend as far as the end plate, a common feature of fetal end plates in mammalia and of tongue muscle throughout life in some amphibia. The situation in the winter frog may, therefore, mean not so much the need of two separate contractile systems as simply a lessening of the stimulus to muscles to hasten their speed of contraction in winter months.

In mammalian muscle there is increasing evidence that histologic, physiologic, and pharmacologic specialization of muscle fibers is determined in part by their ontogeny and partly by their postnatal use. For example, Jewell and Zaimis have recently shown that, whereas red muscle in the cat is very resistant to neuromuscular block by decamethonium, pale muscle is very sensitive. With use-hypertrophy red muscle retains its slowness of contraction and its pharmacologic difference is accentuated, even if it is made to do the work of pale muscle by tenotomy of the latter. In neural atrophy and disuse atrophy, both types of muscle become pharmacologically similar and the color difference tends to disappear.

The process of denervation atrophy appears to be a reversion to the fetal state. In the mammalia denervation atrophy proceeds at different speeds in different muscles, being most rapid and uniform in highly specialized muscles, such as those of the larynx, and slowest in those whose fibers at full maturity are still of small granular fetal type, such as those of the external anal sphincter. In most muscles there are mixtures of fibers undergoing atrophy at different rates, the intrafusal fibers of the muscle spindles being slowest of all. We may expect these differences to correlate with size of medullation of motor nerve fibers, though this has been studied only in relation to the spindles. It is notable that in denervation atrophy the pharmacologic reactions and excitability characteristics of the mammalian muscle membrane revert to those closely resembling the "primitive" fibers of the winter frog.

If then we ask why it is that some muscles show the first symptoms of curare poisoning or of myasthenia gravis and others first show the effects of potassium deficiency, we may point to the considerable differences in specialization of function. The same differences presumably underlie the vulnerability of different muscles to dystrophy according to age of onset and type of the disease and to myositis in relation to type of noxious agent. I have been impressed that even in the same muscle in myoglobinuria there are great differences in the vulnerability of different fibers to dissolution, and this is also true in muscular dystrophy. The differences in nerve ending observed in cases of infantile atrophy by Coers point to delay in maturation.

What are the physiologic stimuli that lead to these different types of specialization of muscle fiber? Since reversion to fetal type is characteristic of neural atrophy, it is natural to look for evidence that nerve supplies some factor to muscle that determines specialization. So far none has been found, though many studies suggest strongly that nerve supplies a growth factor in the maturation stage of amphibia. Muscle fails to degenerate if the nerve is blocked but anatomically intact, but this may be due to the very small "quantal" secretion of transmitter substance now shown to be continually occurring in the absence of "impulses." Coinnervation of muscle fibers of different size and lipid content suggests that these aspects may be independent of nerve, and it is natural to look for associated endocrine factors. Unfortunately all attempts to assess differences related to endocrine deficiency have suffered from an inherent defect. The muscles chosen for study, for example, the perineal muscles of the male rat or the jaw muscles of the guinea pig, are those that are strongly innervated by sexual reflexes. It is not surprising, therefore, to find that castration leads to a partial degree of the same change that occurs with denervation, or that male hormone is ineffective in causing hypertrophy if the muscle is denervated. So far one can only say that the behavioral reflex effects of hormones are more effective on muscle than any direct effect. Hypothyroidism is reported to prolong the muscle twitch but makes no difference to the oxygen uptake, pointing to a change in the duration of some event in the contraction cycle, but to no essential change in the physical mechanism.

The most remarkable general effects in the physiology of muscle are the result of the stimulus of active tension and ischemia in causing hypertrophy, and these are greatly in need of further investigation, for only by knowledge of the physiologic response are we likely to understand chemical sensitivities and pathologic reactions.

MODERATOR: The last speaker, Dr. Raymond D. Adams, Bullard Professor of neuropathology at Harvard Medical School and chief of neurology of Massachusetts General Hospital, will summarize some of the problems of pathology of muscle.

DR. RAYMOND D. ADAMS: The brief period during which I am to discuss recent advances in the pathology of muscle disease allows little time for more than a simple summary of a few articles that have appeared in the last few years. A recitation of this type is certain to be dull and uninspiring unless time were given for a critical evaluation of these recent contributions. Rather than risk the tedium of such a presentation, I propose instead to ask an evocative question concerning one of the most frequent muscle diseases—that of primary muscular dystrophy. This should afford us an opportunity that seldom offers itself of hearing the views of a physiologist, anatomist, and biochemist on the fundamental process underlying progressive muscular dystrophy.

This particular disease stands as the prototype of all diseases of muscle. It was the first one described and has been subjected to the close scrutiny of clinicians and pathologists for many years. Nevertheless, it must be conceded that we have learned neither its cause nor the mechanism involved.

The primary abnormality of the muscle in

dystrophy has been peculiarly elusive. Duchenne, Erb, Heidenhain, and many contemporary investigators have attempted to determine its nature. The genetic origin is indisputable. The long period during which muscle structure and function remains normal, giving way to progressive weakness and wasting of the musculature of shoulder and pelvic girdles, the trunk, parts of the proximal limbs and sometimes the face, without sign of nerve or spinal cord disease, suggests that some biochemical defect long antedates the obvious pathologic change in muscle. Expressed another way, one would suppose that the disease existing from birth only gives rise to paralysis and visible changes in the muscle in its most advanced stages. Biochemical studies, however, have succeeded in demonstrating little more than a reduction in the total functioning muscle mass and have thrown no light on the primary abnormality.

In any well chosen microscopic section of dystrophic muscle, the following abnormalities can be demonstrated.

1. Loss of many of the muscle fibers.
2. Degeneration and phagocytosis of a few muscle fibers.
3. Alteration of muscle fibers.
   a Enlarged fibers with central nuclei.
   b. Small muscle fibers.
   c. Fibers with abnormalities of structure — rows of central nuclei, loss of peripheral myofibrils, or distortions of myofibrils.
4. Paucity of regenerative changes — nuclei, sarcosplasm, or myofibrils.
5. Increase in connective tissue between fibers.
6. Presence of many fat cells between single fibers or fascicles of fibers.

It is generally agreed that loss of fibers is the explanation of much of the clinical picture, but how does it come about? Erb conceived the essential process to be one of hypertrophy followed by atrophy with vacuolization and splitting of fibers. Although this provides an explanation of large and small fibers, it fails to account for the degenerative change. Others have singled out the muscle fiber degeneration as the primary change, but this leaves us without an explanation for the enlargement and atrophy, unless the former change is one of work hypertrophy and the atrophy is the result of splitting or regeneration of buds from the healthy ends of degenerating fibers. Atrophy and a lack of ability of sarcolemmal nuclei to maintain the sarcoplasm or myofibrils have been proposed. This series of changes also leaves us without an explanation of the degeneration of the large fibers with central nuclei. The fibrosis and lipomatosis are usually assumed to be secondary to the changes in the muscle fibers and the loss of fibers.

How can the problem of the primary change be resolved? Probably only by the study of the isolated cell under conditions that are reasonably controlled, taking note of the resting electrical potential of the fiber, its biochemical activity, its capacity to develop, to regenerate after injury, and to reproduce itself in tissue culture. The dystrophy which has recently been found in a strain of mice in the laboratories at Bar Harbor, Maine, may throw some light on these problems because it can be studied at all stages of the disease.

From the study of experimentally injured dystrophic muscle and from some biopsy specimens, we are inclined to believe that the small fibers are formed by the branching and forking of damaged ones. Enlargement of fibers may well be the result of work hypertrophy of the sound fibers, though the central nuclei cast some doubt on this explanation. In our opinion, therefore, degeneration is the most definite and important change. The lack of successful regenerative activity cannot be explained. The studies of Walton indicate that the sound muscle fibers in the dystrophic patient are capable of reacting to physical injury by the usual sequence of sarcolemmal nuclear proliferation, basophilia of sarcoplasm, and regeneration of myofibrils. It is difficult to determine the reaction of atrophic fibers to injury, but presumably the regenerative potential of the dystrophic fiber to injury is not significantly altered. Another equally tenable opinion would be that degeneration, atrophy, and hypertrophy are all manifestations of the fundamental process which exerts a variable effect depending on its intensity. In other words, the process may cause either immediate death or possibly progressive atrophy and ultimate disappearance of the muscle cell.

This problem of the fundamental change in the dystrophic fiber has been studied in recent years by the electron microscopist, the biochemist, and the physiologist. I would like to have each of my colleagues give us his views of this disease and the contribution that has come from the application of these special methods.

QUESTIONS AND ANSWERS

MODERATOR: Dr. Gunnard Wohlfart, professor of neurology of the University of Lund, Sweden, who is our distinguished guest, has consented to ask the first question.

DR. WOHLFART: I would like to ask about two different things. First, in polymyositis, I would like to learn more about the different types of etiology, the different types of course, and something of the pathology. Secondly, I would like to learn about the three different types of hereditary muscle degeneration, namely, ordinary muscle dystrophy, distal myopathy, and myotonic dystrophy. I would like to learn a little about the differences in pathology in these three disorders.

DR. ADAMS: The first question regarding the different types of polymyositis with pathologic changes: I would say first off that I think there can be no doubt that there is a very definite clinical and pathologic entity that is called polymyositis. I think all of you are familiar with the principal clinical changes. The pathology is quite characteristic in many cases, consisting of a very pronounced degenerative change in the muscle fibers far in excess of what one ordinarily sees in even the more rapidly advancing dystrophies—and a very brisk regenerative activity on the part of the remaining fibers and very definite and fairly pronounced infiltrations of inflammatory cells in the endomysium and around the blood vessels. I think that this particular pathologic and clinical entity is very closely linked to collagen disease. Of more than 40 cases that we have had at the Massachusetts General Hospital, 26 had or ultimately developed some other form of collagen disease. I feel that we are in serious trouble in diagnosis from pathologic material in a certain number of cases here, however, because there is no doubt but that fairly typical cases clinically may have little or no inflammatory cell reaction and may go into a rather chronic stage where the degree of muscle fiber degeneration is rather slight. On numerous occasions in the last few years, I have felt defeated from the study of a pathologic specimen, being unable to decide whether it was a chronic polymyositis or a rapidly advancing muscular dystrophy. This tells us that the pathologic study with an ordinary light microscope has grave limitations, and the changes often acquire significance only when taken into relation to the total clinical picture. There are several other polymyopathies where inflammatory cell reaction is lacking, where muscle fiber degeneration is pronounced, where there may be mild myoglobinuria and even death from lower nephron nephrosis that should be distinguished from this group of polymyositis or dermatomyositis. This is a chapter of muscle pathology that has yet to be written, I am sure.

Dr. Wohlfart could much more ably expound on the differences between myotonic dystrophy, the distal dystrophy of Gowers and Weelander and Aldon Turner, than any of us here, because they have had so many more of those cases in Sweden than we here. I feel, with respect to myotonic dystrophy, that the degree of proliferation of centrally placed sarcolemma nuclei is far in excess here to that which you see in most cases of muscular dystrophy. Many of the other changes are much the same. The real problem that the pathologist faces here, and which we are not at all agreed upon among ourselves, is how many of the changes that we see in the remaining fibers are really true changes that reflect this metabolic abnormality going on in the muscle, and how many of them are artifacts produced by the biopsy of irritable muscle, the placing of it in fixative, and so on. I think all pathologists would agree that, when one finds vacuoles, disruption of myofibrils, alteration of sarcoplasm without cellular reaction, and distortion of myofibrils, one becomes uncertain as to the significance of these changes. These alterations seem to be more pronounced in biopsy material from myotonic dystrophy because of its exceptional irritability. I have had very little experience with distal dystrophy and I am sure that our material will not permit us to draw out any of the differences between this and the other forms.

DR. DENNY-BROWN: I agree with Dr. Adams that such differences as may be seen between dystrophies are quantitative rather than qualitative. In some, as he has mentioned, the nuclear proliferation is much more remarkable. In others, differences in fiber size and twinning of fibers are more commonly seen. But, if you take any one histologic criterion, then it is in some degree present in all types of muscular dystrophy that I know of.

DR. WOHLFART: I would like to ask whether Dr. Adams thinks that the dystrophic form of myotonia is the tonic form of myodystrophy, or is it a different disease?

DR. ADAMS: That is a very pointed and extremely difficult question. The electromyographer is turning up with increasing frequency myotonic reaction in single fibers in all types of dystrophy, which raises the question whether there is merely a quantitative difference between the myotonia that you see and the advanced myotonic dystrophy and the ordinary muscle dystrophy. I think Dr. Denny-Brown might have more to say about this.

DR. DENNY-BROWN: Only to say that I have not seen true myotonia in other types of dystrophy, Dr. Adams.

DR. ADAMS: Not in the electromyograms? I know you have been critical of some electromyography that has issued from various laboratories, but it seems to be turning up with increasing frequency.

DR. DENNY-BROWN: I think that in this connection it is very important to define what you mean by myotonia. Myotonia in the sense of a series of very small action potentials of the size of those of a single muscle fiber, provoked not by one excitation of the muscle, but by more than one as if by a cumulative chemical effect, for me is unique in conditions of dystrophia myotonica and congenital myotonia. A number of conditions will set up a train of action potentials in isolated muscle fiber, but they set them up immediately following the excitation, as for example produced by 2-4-D Veratrin and other chemical substances. But the delay in response is what is so peculiar to myotonia. Microelectrodes, unfortunately, magnify the movement artefact that contaminates all electrical recording from muscle, and I cannot accept "myotonia" recorded only by such means.

MODERATOR: Dr. Bennett, do you have a question that you would like to ask of the other members of the panel, and would you like to respond to either Dr. Wohlfart's question or to the ones posed by Dr. Adams?

DR. BENNETT: Perhaps I may be permitted to comment that, if one is searching for morphologic changes associated with disease, the light microscope, which Dr. Adams used, really gives us little information and conceals a great deal. I might ask you to contrast his pictures with the detail which one sees in the electron micrographs, where one can see definitely outlined mitochondria with elaborate internal detail, along with many details of sarcoplasmatic structure. One also sees intricate longitudinal and cross patterns of filaments within the myofibril and many other details which were not shown here today. So the use of hematoxylin and eosin or even Masson stains with the light microscope by no means exhausts the tools at our disposal for exploring the structure of muscle. It becomes evident that, if one wishes to get the additional information, one must pay the price and learn to use the tools.

DR. ADAMS: That brings me to pose my question once more: There have been several electron microscopic studies of dystrophic muscle. Would you review those, Dr. Bennett, and tell us what information they give us?

DR. BENNETT: There have been some electron microscope studies of other types of degeneration of muscle also. The studies with which I am most familiar are from our own laboratory, by Dr. Hampton and Dr. Rumery. These are not yet published. It seems evident that one of the earliest changes which one can detect is disorganization of the filaments within the myofibril. The mitochondria appear to live a fairly long time in the degenerating muscle fibers, at least in the samples which I have seen. I think that an evaluation of this material poses difficulties, however. One of the foremost lies in the trouble which one encounters in judging the validity of sampling of the tissue which one is examining with the electron microscope. One sees only a very small portion of the material at a time. One can study profitably small bits of tissue, perhaps not more than a tenth of a millimeter in diameter. One can cut many thousands of sections within a single block of this size. The section thicknesses which are used are the order of 200 to 500 Angstrom units, or somewhere in the neighborhood of a twentieth of a micron. Thus one examines a very small sample of the tissue. Though one can get a good deal of information about that sample, it is difficult to evaluate this in terms of the whole structure. I do not think that any of the studies which I have seen have carried the problem far enough or have met these uncertainties satisfactorily.

DR. DENNY-BROWN: I would like to ask Dr. Bennett if he has any information as to the location of myoglobin in the electron microscope picture.

DR. BENNETT: No. This is primarily, I think, a problem for spectroscopy. I rather imagine, as Dr. Denny-Brown told us, that myoglobin is distributed in the sarcoplasm, but, with the recognition of the organization of sarcoplasm, the question rises whether further information relating to its distribution would be helpful. There are some substances in muscle—glycogen, for example—the distribution of which has been worked out at the electron microscope level rather nicely by Dr. Fawcett and by others. Often there appears to be no preferential distribution of the glycogen within the fibril, at least at the level of organization relating to the sarcomere bands. There is light microscope evidence by Manicini and others that is in conflict with this. Perhaps the most favorable material for study of myoglobin distribution might lie in the muscles of diving

animals, such as whales and penguins or perhaps seals, where very large amounts of myoglobin are present. If any of you can recall reading *Moby Dick*, you may remember that the capacity of the whale for storing very large amounts of air within its body was recognized by Herman Melville. He describes the killing of the whale in physiologic terms, relating the slaughter to a process of forcing the whale to exhaust himself of oxygen by making him take a series of dives. It takes about 70 breaths, consuming 11 minutes, I believe Melville says, for a sperm whale to load up completely with air once he surfaces from an exhausting dive lasting an hour or more. So it is important to harpoon him when the whale surfaces before he takes his full complement of 70 breaths. He is then forced to dive with an incomplete load of oxygen and can't go so deep or so far. Hence when he surfaces the next time one can get at him sooner. I suppose that a sample from one of Melville's whales would have been very favorable material for answering Dr. Denny-Brown's question.

MODERATOR: Dr. Szent-Györgyi, do you have a question that you would like to ask the panel? Or would you like to pose an answer to Dr. Adams' question?

DR. ADAMS: What do you consider the primary change to be and the most likely change in progressive muscular dystrophy?

DR. SZENT-GYÖRGYI: I haven't the least idea.

DR. DENNY-BROWN: May I ask Dr. Szent-Györgyi whether contractile activity of actomyosin has ever been found to be associated with electrical change, and if acetylcholine can provoke its contraction?

DR. SZENT-GYÖRGYI: No, there is no reaction between acetylcholine and actomyosin. There have been theories proposed but the lifetime of these theories is about six months and none of them has survived. I don't think that acetylcholine has anything to do with actomyosin directly. Dr. Denny-Brown asked about acetylcholine contracture. Even then I could not believe that acetylcholine acts on actomyosin and for the very simple reason that we can produce contracture with very little acetylcholine, so there wouldn't be one molecule of acetylcholine for one molecule of actomyosin. The basis of any direct interaction is chemical. One particle of one must act on another. Acetylcholine is active in such a small quantity and there is so much actomyosin that any direct interaction, to my mind, is impossible. There must be an amplifier between them. So I think that acetylcholine may let in the potassium or sodium to act as an amplifier, because there are so many of those ions.

MODERATOR: A question from the floor is directed to Dr. Szent-Györgyi. What is your present concept or your current thoughts about the process of relaxation in myofibrils?

DR. SZENT-GYÖRGYI: As I tried to point out—the muscle is at rest because there is no actomyosin. The actin and myosin are separated just a very short distance, so relaxation must be a parting of the two again. What happens in the whole cycle of contraction is that something happens, which we don't know what it is, which I believe is an electric field that brings actin and myosin together. As soon as they are together, actin, myosin, and ATP have to go into the contractive state, and in this contracted state ATP loses one phosphate. That one phosphate is very important for the relaxation for pushing them apart again, because it means two additional valences, two additional electric charges. So the excitation comes along, there is some change which we don't know what, a very, very temporary change which lasts only very shortly, and then as a consequence of this change, "A" let us say, actin and myosin get together and they contract and ATP becomes de-phosphorated. Now in order for actinomyosin to part again, the ATP must regain its phosphate. And the essential point is rephosphorylation of ATP. Then the change "A" has already passed. This very temporary change "A" brings actin and myosin together and now, since the primary change passed, they could part again immediately but they can't because ATP has lost a phosphate. As soon as ATP regains the phosphate they can part again because then we have only two conditions. So now they could part but they can't part because ATP has lost its phosphate, but as soon as ATP regains the phosphate then they can part again and there is relaxation.

MODERATOR: Dr. Denny-Brown, I have several questions directed to you. What role does the gamma circuit play in the initiation of a willed movement? Is there an intrinsic cord mechanism which inhibits or facilitates the firing of the gamma circuit? Is there any way to study the activity of the gamma circuit in human beings?

DR. DENNY-BROWN: This takes us a long way from consideration of muscle as a tissue. But the question certainly is a very practical one in relation to the energy of setting up a muscular contraction, which certainly can be derived from muscle spindle activation centrally

reflected to the regular motor neurons of the muscle concerned. I know of no way of approaching this question in man, because the study of gamma innervation of the muscle spindles has been only in terms of dissecting individual dorsal roots to find the small specific efferents to muscle spindles and to record directly from them.

MODERATOR: A question in two parts: What is the explanation of the slowness of contraction in denervated muscles? What is the explanation for the monophasic positive wave in denervation? This is directed to Dr. Denny-Brown.

DR. DENNY-BROWN: I have explained the primitive type of response in denervated muscle fiber, and its resemblance to the response of the nondenervated "slow muscle fiber" of Kuffler. The reason for this slow response and of the monophasic potential that accompanies it is this lower polarization of the membrane of the slow muscle fiber which has a polarization of around 40 microvolts, as opposed to 70, 80, or 90 or more in fast types of muscle fiber. I suspect that further studies will show all grades of fiber in many muscles and not just two types. This would mean that these differences represent various grades of a dynamic adjustment to physiologic need and not the existence of two categoric motor functions.

■ For many diseases each man will have to make his own types; everybody does so consciously or unconsciously, but I submit that we should make them consciously and definitely. Taking for next illustration migraine: I make three types, or rather consider cases of it as they are, (1) typical, (2) subtypical, and (3) supertypical. (1) A typical case is one in which there is "visual projection," the well-known zigzag or "fortification" outline is most common, with, in most cases, a hemianopic area; then comes headache, most often frontal and one-sided, and lastly vomiting. (2) There are subtypical cases, visual projections and nothing more, or headache unpreceded by visual projections and nothing more, or headache unpreceded by visual projections, and not followed by vomiting. (3) There are supertypical cases deserving very particular consideration. In these there is in addition, so to say, to the other symptoms, numbness of one side of the body, and when the numbness is of the right side there may be also considerable aphasia. To the inexperienced these cases look far more serious than they are; they do not point to any gross local disease. Some of the symptoms of migraine, the headache among others, are, I think, after-effects of the discharge producing the paroxysm.

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.

Neurology at the Crossroads

G. H. Monrad-Krohn, M.D.

NEUROLOGY has found itself in the past and no doubt will find itself in the future at many crossroads, and at each crossing the problems will probably be different and not necessarily the same as the ones facing us today. Knowledge in medical science rarely reaches a final stage. Progress and development continue, both in knowledge and in technics. The latter in particular create certain dangers, since special technics require special training which may become so complicated as to obscure the principal purpose of the procedures, namely furthering our knowledge and understanding of the nervous system. In a general way, we may postulate that the future of neurology will depend upon its ability to assimilate the various special technics of today and of the future in a harmonious and balanced manner, without losing sight of the orientation and survey of neurology as a whole which obviously is indispensable for the necessary coordination of the various subdisciplines.

The best assurance that the field of neurology will develop properly is to make sure that all workers in the field are properly trained in neuroanatomy, neurophysiology, and, last but not least, clinical neurology. In future neurology we do not want one-track men who, in neuroradiology, for example, forget necessary considerations to the patient for the sake of a good picture. Nor has neurology very much use for investigators who, in their excellent technical work on the electrical registrations of various functions of nervous structures in animals, lose sight of *homo sapiens* in his likenesses and differences from the experimental animal. Nor has neurology much use for such clinicians who, in their hunt for clinical curiosities (and priorities), lose sight of general anatomic and physiologic problems. In this connection, I should like to add that the value of old curiosities depends on the light they may throw on general problems. At all times our chief aim, however, should be to apply newer information regarding neuroanatomy and neurophysiology to the clinical aspects of neurology in order to attain a more rational and fruitful basis for therapeutics. Talking of therapeutics, I should like to point out that we may soon have still another form of neurologist, namely the pharmaconeurologist or the neuropharmacologist.

It is apparent that I am strongly opposed to placing neuroanatomy and neurophysiology as well as other basic sciences in neurology too far out in the periphery of our sphere of interest. To my mind, these disciplines are central, important, and integrating parts of neurology. To my mind, the discovery of ascending fibers in the pyramidal tract is more important than many descriptions of weird clinical curiosities, and the minute study of the oligodendrocytes—their origin and function—may probably be of equal or more practical value for our understanding of demyelinating processes than descriptions of the various unusual clinical varieties of multiple sclerosis. The International Congresses of Neurology have always fostered the importance of the basic fields of neurology, and at the first congress held in Bern in 1931 one of the most outstanding, never-to-be-forgotten contributions was Hess's description and kinematographic demonstration of experimental sleep in animals. I shall never forget it.

However, in spite of the importance of basic neurology, one cannot overlook the sovereign position of the neurologic clinic, particularly since in recent years the clinic has been unjudiciously dethroned and there has developed a lack of balance between the different branches of neurology. Minute clinical observation and examination still have much to learn and much to give.

For the future of neurology, then, I consider it necessary that all present and future subdisciplines be assimilated in a harmonious and well coordinated way. But this is not done by calling our international meetings "Congresses of "Neurological Sciences," a most unfortunate name which only accentuates the dismembering of our science. To my mind, it recalls Shelley's words, "Human pride is skillful to invent most serious names to hide its ignorance."

Contribution to the Round Table Conference on the Future of Neurology at the Sixth International Congress of Neurology, Brussels, July 27, 1957.
Holmenskolveien 5, Smestad, Oslo, Norway.

In some ultraspecialized quarters such human pride and prestige may sometimes thrive too well.

It will be an advantage to revert to the old name for our congresses, that is, "International Congresses of Neurology," where neurologists of all shades can discuss neurologic problems from different technical experience.

At the Paris congress in 1949, some of us urged that the therapeutic side of clinical neurology be given more attention. This has undoubtedly borne fruit in many quarters, particularly with regard to reeducation and rehabilitation. Yet, I still think that in many quarters the therapeutic side of our science might be given more attention, not only in our daily work, but also at our meetings. Our therapeutics consist not only in neurosurgical handicraft and in old and new methods of reeducation and rehabilitation but also in pharmacologic treatment. The pharmacology of the nervous system is a branch of our science which is now in rapid growth, and we should, therefore, welcome neuropharmacologists in our midst and try to coordinate this important branch with the rest of neurology.

Finally, I should like to mention that, to my mind, neurology has still a duty to fulfill toward the psychoneuroses and their many problems. Today when the word "psychosomatic" is shouted at every street corner, it should not be forgotten that there are also many "somatopsychic" processes and conditions which also need elucidation and treatment. To be more explicit, I fully realize that there are many psychosomatic conditions where psychic factors lead to somatic disturbances. But there are also many somatopsychic conditions where primary somatic lesions (often perhaps undiscovered) lead to secondary psychic disturbances (and also many cases with a mixed etiology of psychic and somatic factors). I have a feeling that the catchword "psychosomatic" has in many quarters warped the balanced judgment regarding this borderland. When we consider what a multitude of disease processes since Charcot's time have been transferred from the category of "functional diseases" (largely believed to be psychosomatic) to that of primary somatic processes, it would be unwise to believe that this development has reached final results. In the past neurology has contributed greatly to such transfers. In the further elucidation of this important borderland, neurologic research still has a scope—and, therefore, also a duty.

■ The two great causes of tetanus are, as has been mentioned already, cold and damp, and bodily injury of some sort. Exposure to cold and damp tells most in this manner when acting upon a body previously relaxed by heat and perspiring, and this is all that can be said, except that this exposure is more likely to issue in tetanus in a foul atmosphere than in a fresh one. As regards the hurt which may give rise to tetanus, it is difficult to know what to say. In the Peninsular war, as Sir James McGregor states, tetanus supervened on every description and in every stage of the wounds, from the slightest to the most formidable, in the healthy and sloughing, the incised and lacerated, the most simple and the most complicated; and this statement expresses the opinion of all surgeons, army-surgeons and others. Indeed, all that can be said is that punctured wounds seem to be more likely to issue in tetanus than excised, and wounds in the extremities more than wounds in the head, breast, and neck. And certainly an inflammatory condition of the wound cannot be regarded as essential. In a great number of cases, in the majority perhaps, the primary wound was completely healed and almost forgotten when the symptoms of tetanus made their appearance.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

CASE REPORT

Sarcomatous Degeneration of Osteitis Deformans Causing Compression of the Cauda Equina

Bernard E. Finneson, M.D., Bernard Goluboff, M.D. and Henry A. Shenkin, M.D.

PAGET'S DISEASE (osteitis deformans) is found in 3 per cent of autopsies on persons over 40 years of age,[1] but spinal cord compression secondary to this disease is relatively rare, 56 cases having been reported previously.[2–4] Spinal compression due to sarcomatous change of osteitis deformans has not been noted in our survey of the literature.

REPORT OF A CASE

A 64-year-old white female was admitted to the Albert Einstein Medical Center on June 7, 1956 with a four-year history of low back pain with radiation of pain into both lower extremities of four weeks' duration. With the onset of pain radiating down her legs, the patient noted stiffness and weakness of the lower extremities upon arising in the morning, which improved as the day progressed. The patient herself had noted no change, but she had been told by friends and family that she appeared markedly shorter in recent years.

Examination revealed marked tenderness to pressure over the lumbar spine; the lumbar curvature was greatly increased. Complete roentgen survey revealed advanced changes of Paget's disease involving the left femur, right ilium, right humerus, lumbar vertebrae, and the sacrum. The L_4-L_5 and L_5-S_1 joints were markedly narrowed. Shortly after hospitalization, the patient stated that her pain had improved markedly and she expressed eagerness to return home. She was discharged on June 15, 1956.

At home the pain in the low back and lower extremities became progressively worse and it was necessary to re-hospitalize the patient on June 22, 1956. On re-admission she was noted to expectorate blood-tinged sputum. This symptom, it was learned, had developed during her initial hospitalization but, in her desire to prevent a delay in discharge, the patient had withheld this information from the medical staff. In addition to pain, the weakness of both lower extremities had advanced to the degree that she was unable to walk and she now complained of severe malaise. Portable roentgen examination of the chest revealed multiple nodular shadows distributed throughout both lung fields. This was interpreted initially as evidence of pulmonary congestion and probable infarction, but this interpretation was subsequently changed to neoplastic metastatic disease.

On July 11, 1956 the patient was seen in neurosurgical consultation. At that time she had weakness of both lower extremities, the right greater than the left, associated with severe tenderness of all muscle groups. The deep tendon reflexes were absent in the lower extremities. Painful sensation was diminished over the medial anterior aspect of the right leg and position sense was absent in both feet. The impression at that time was that the patient had a rapidly advancing peripheral neuropathy. A lumbar puncture was performed at the L_1-L_2 interspace on July 13, 1956 and revealed a pressure of 30 to 40 mm. of water, with prompt rise and fall on jugular compression. On the morning of July 14, 1956, the patient was found to have urinary and fecal incontinence associated with a complete motor paralysis of both lower extremities. All sensation was absent below the L_2 segment. Shortly after paraplegia was noted a myelogram was performed. This revealed a complete block at the level of the second lumbar vertebra. Pantopaque flowed freely without obstruction or filling defect in the cervical and thoracic regions.

Because of the reluctance of the family and patient to consent to surgery, laminectomy was delayed until the day following onset of paraplegia. At operation the spines and lamina from L_2 to L_5 were found to be grossly involved by Paget's disease. These lamina were completely fused and gave the appearance of a solid sheath of bone. This bone was of softer consistency than normal and bled copiously when bitten into with a rongeur. Beneath the involved bone, soft greyish tumor tissue of a spongy consistency was encountered. The tumor did not appear to involve the dura. Upon removal of the epidural tumor tissue, the dura began to pulsate. Immediately after surgery the patient noted marked relief of pain and there was good return of sensation within three days. The motor power in her lower extremities improved slightly, but there was no improvement in sphincter function postoperatively. The patient was discharged to her home on July 28, 1956 and died one month later. A postmortem examination was not performed. Microscopic examination of the tissue removed at surgery showed that the fragments of bone had undergone changes typical of osteitis deformans. The tumor tissue was identified as osteogenic sarcoma (figures 1–4).

COMMENT

Sir James Paget, the English surgeon who first described this disease as a clinical entity

From the departments of neurosurgery and medicine, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

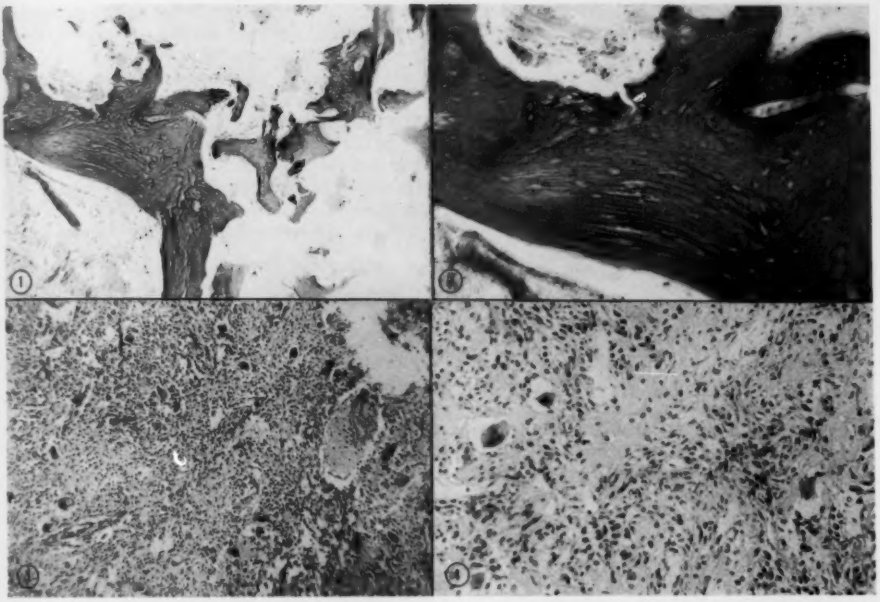

FIG. 1. Bone in Paget's disease showing mosaic pattern of cement lines and uneven scalloped margins due to alternating bone formation and destruction. The marrow is replaced by loose vascular connective tissue.
FIG. 2. High power field.
FIG. 3. Osteogenic sarcoma with giant tumor cells (dark nuclei) and osteoclasts (large, pale, multinucleated cells at lower right of center).
FIG. 4. Area of osteogenic sarcoma (upper left) with poorly formed osteoid tissue (upper central) and three osteoclasts (left).

in 1877,[5] believed the bony changes were related to an inflammatory process. Because the chief clinical manifestation was the deforming nature of bony changes, he called the disease "osteitis deformans." In 1889 he wrote a paper[6] dealing with the relationship of osteitis deformans and osteogenic sarcoma. His study was based on the observation of five cases of cancer or sarcoma developing in 23 patients having osteitis deformans, and he concluded that he could not venture to guess what the nature of the connection was between the two diseases. Present opinion does not favor an inflammatory process as the cause of Paget's disease but, despite numerous and periodic reports in the literature on osteitis deformans, little has been added to our knowledge of the etiology of this condition or its relationship to osteogenic sarcoma.

The incidence of sarcomatous degeneration in Paget's disease varies according to different observers.[7] Some estimates are as follows: Sear,[8] 2 per cent; Geschickter and Copeland,[9] 5 to 7 per cent; Packard and associates,[10] 7.5 per cent; Gruner and associates,[11] 9.0 per cent; DaCosta and co-workers,[12] 9.5 per cent; Bird,[13] 11 per cent. Several series of osteogenic sarcoma occurring in Paget's disease have been reported more recently.[14–16] The average age of patients having this complication is 60 years, and males appear to be afflicted more commonly, as has been noted also in patients suffering with osteogenic sarcoma that occurs independently. An elevated alkaline phosphatase is the rule, the average figure being 42 Bodansky units. It has recently been pointed out that pulmonary metastasis is common, developing in 11 out of a reported series of 19 patients.[15] Osteogenic sarcoma, when it develops in osteitis deformans, is found only in the involved bones but may occur in several bones simultaneously.

In evaluating the cause of this patient's neurologic symptoms after the development of paraplegia, malignant neoplastic degeneration was suspected principally because of the highly suspicious chest film. This preoperative impression was augmented by the site of the

compression. Although osteitis deformans involves the lumbar spine more frequently than the dorsal, when spinal cord compression occurs as the result of osteitis deformans it develops almost always in the dorsal region. The probable explanation for this predilection is that the smallest cross-sectional area of the spinal canal is in the thoracic region and, therefore, any proliferation of the bony vertebral ring would be more apt to manifest itself by spinal cord embarrassment at this level.[17] The rapid onset of paraplegia was also of value in indicating that the compression was caused by a rapidly expanding neoplasm as opposed to simple Paget's disease. The vast majority of reported cases of compression due to osteitis deformans had chronic development of symptoms, with only an occasional report of acute onset of neurologic symptoms.

With regard to surgical technic, greater than usual care is required in performing bilateral subperiosteal paravertebral muscle dissection when the underlying lamina are involved by Paget's disease. There is an increase in vascular attachments between the paraspinal muscles and diseased lamina, and direct downward pressure with the periosteal elevators may fracture a softened lamina and damage the underlying neural elements. The blood flow through bone affected by osteitis deformans has been measured and found to be increased many times over that of normal bone.[5] This observation is well confirmed by the difficulties in achieving adequate hemostasis during the performance of the laminectomy.

SUMMARY AND CONCLUSIONS

A known case of Paget's disease developed acute onset of cauda equina compression syndrome. At laminectomy the cause of the compression was seen to be osteogenic sarcoma arising in bone involved by osteitis deformans. Roentgenographic evidence of malignancy in the chest, the site of compression in the lumbar rather than the thoracic vertebrae, and the acute onset of symptoms were factors that differentiated the malignant neoplastic nature of the compression from Paget's disease.

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Neurology

BOOK REVIEWS

The Epileptic Seizure

Cosimo Ajmone-Marsan, M.D. and Bruce L. Ralston, M.D. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 251 pages. $6.00.

ALTHOUGH bearing the hallmark of the Montreal school, this study derives from the branch of electroencephalography and clinical neurophysiology of the National Institute of Neurological Diseases and Blindness. In the main, an effort is made to describe objectively convulsions activated by Metrazol in patients admitted to the epilepsy unit for the study of intractable seizures. Data upon 119 such cases is included, 52 of which were classified as having a unilateral or a bilateral temporal origin. Electroencephalographic tracings done simultaneously permit inferences concerning the ultimate cerebral origin of particular sequences of seizure and the routes of spread from different epileptogenic foci.

A valuable review of the Metrazol activation literature is provided. This is developed with respect to methods of intravenous administration and dosage, body weight, threshold of activation, criteria for interpretation of electroencephalographic changes, and results of activation in control as compared with epileptic patients. In the majority of cases reported, Metrazol injection was continued until a seizure resulted; data are presented on pre-ictal paroxysmal, immediate pre-ictal, ictal, and post-ictal changes, and on the relations between electroencephalographic signs of activation and the sequence of development of a seizure.

Phenomena of note observed during the usual two minute ictus were: tonic postural alteration, full or larval (M2e); unilateral tonic facial contraction (UTF); ictal focal clonic activity; ictal aphasia; head turning; eye movements; automatism; and generalized tonic-clonic convulsion (GM). Under seizure pattern formulae, the sequence in which these may appear is evaluated as an aid in deciding the localization of an epileptogenic focus. For example (p. 127), "The elimination of an initial automatism from the seizure formula of M2e, UTF, and GM radically alters the diagnostic significance in terms of localization, but not lateralization of the discharge. The emphasis in localization switches to above the Sylvian fissure with the frontal-supplementary and supplementary groups being most prominent, and next, the parieto-occipital." In this fashion the writers weigh the significance of different formulae in determining the site from which activated seizures spread. Their classification includes temporal (uni- and bilateral, and questionable), anterior frontal, frontal supplementary, supplementary motor, central, parieto-occipital, unlocalized, and centrencephalic.

The Jasper "10-20 system" of recording was used, and numerous tracings are illustrated. More often than not, the labels are too small to be legible and the tracings themselves sometimes suffer from excessive reduction in printing. References to electrocorticographic confirmation of the sites from which seizures were presumed to spread are alluded to infrequently. One is left with the impression that seizure formula plus scalp recorded tracings were the principal determinants of localization.

Although research emphasis is primary, the book contains material of practical value to those who use Metrazol activation as a prelude to the surgical treatment of intractable seizures. For others, the relatively high price for a book of limited scope suggests inspection of contents.

J. L. O.

Methodology of the Study of Ageing

Edited by G. E. W. Wolstenholme and Cecelia M. O'Connor. Ciba Foundation Colloquia on Ageing. Volume 3, 1957. Boston: Little, Brown and Company, 202 pages. $6.50.

THIS VOLUME, another in the now familiar series of Ciba Colloquia, presents 12 papers on modes of investigating the problems of gerontology. The experienced reader of the Ciba studies will always include the informal discussion which follows each presentation as a source of much curious and colorful information.

There are several studies on the life span of various animals and an account of the reaction of rats to standard stimuli at different ages. As to human application, there is a paper utilizing adaptability as a criterion of youthfulness; this concept is comprehensive and includes such an elemental factor as the varying adaptability to temperature from infancy to old age. Methods of studying nutrition, genetics, behavior, performance, and intelligence with reference to the aging process are presented.

There is a great deal of lore in the folk tradition and in general literature on the subject of growing old, much of which, as Ward Halstead has recently pointed out, is uncritically accepted by people and some of which proves to be erroneous when subjected to critical studies and evaluation. All animals, apparently, may suffer from characteristic diseases which shorten their life span; a reading of these collected essays, however, indicates that there is very likely in all living things a period of nonpathologic senescence in which aging follows a pattern typical of the species and terminates finally in natural dissolution or death. One could suppose that the practical goal of an inquiry like this is to clear the organs of all extraneous disease processes so that a man would arrive at a state of natural senescence.

This book is nicely edited and, because of the conversational tone of portions of it, especially interesting to read.

A. R. V.

Pneumoencephalography

E. Graeme Robertson. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 482 pages. $14.50.

THIS BOOK by a distinguished clinical neurologist is an outstanding contribution to the literature on pneumoencephalography. It is based primarily on the author's broad personal experience in the field and it reflects his own findings and opinions. Despite this, there is an ample bibliography. The reproductions appear not to have been retouched and are supplemented by line drawings.

The first nine chapters are devoted to problems of anatomy, radiology, and the mechanics of pneumoencephalography. Included is a complete consideration of the mechanisms of ventricular and subarachnoid filling with gas, the applications of these principles to practice, the reasons for failure of filling, and corrective measures to be taken.

Chapters 10 to 20 review the problems of pneumoencephalographic diagnosis according to regions. Each region is discussed from the aspects of radiographic anatomy, normal appearance, roentgen-ray projections used, measurements available, and pathologic appearances. The posterior fossa, aqueduct of Sylvius, third ventricle and neighboring cisterns, suprasellar region, lateral ventricles, and subarachnoid spaces are discussed individually.

The author emphasizes the value of subarachnoid as well as ventricular filling in the diagnosis of lesions of the posterior fossa. Emphasis also is placed on the value of pneumoencephalography in decision as to the best operative approach, ramifications of the tumor, completeness of removal, and nature of a lesion in the suprasellar region. Particularly impressive is his description of how to decant gas into the ventricular system to fill the third ventricle or into the subarachnoid spaces to outline the suprasellar region at will. There is a short chapter on the use of tomography.

Chapters 21 to 25 are utilized to discuss the application of pneumoencephalography to certain neurologic disorders, including atrophic lesions, vascular disease, injuries to the head, infections, and hydrocephalus. The difficulty in establishing satisfactory criteria for atrophy on pneumoencephalographic grounds is discussed.

The next two chapters are devoted to pneumoencephalography in children and to developmental anomalies. These chapters are outstanding. In the final chapter, the author takes a thoughtful look at the value of and indications for pneumoencephalography.

J. R. B.

New Research Techniques for Neuroanatomy

A symposium. Edited by William F. Windle, M.D. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 98 pages. $4.75.

THIS SYMPOSIUM, sponsored by the National Multiple Sclerosis Society, offers nine papers on modern methodology in neuroanatomy and announces, by inference, a new and dynamic era in the study of the morphology of the nervous system.

Electron microscopy in neuroanatomy is presented by Sanford L. Palay; he notes that it is already exercising a maieutic influence on the birth of cytologic concepts. Nauta describes in careful detail the silver impregnation of degenerating axons, adding a new tool for the tracing of conduction pathways. Grant L. Rasmussen describes a selective silver impregnation of synaptic endings and illustrates the method with photomicrographs revealing synaptic terminals in astounding clarity. Tissue culture studies of neural tissue is the subject of Margaret Murray who presents an historic background and illustrates the current status with a review of her work on the effects of drugs on living oligodendroglia. Louis Sokoloff describes physiochemical technics for determining local cerebral blood flow and his studies on relating it to functional activity. The localization of enzymes in nervous tissue is discussed by George Koelle, and the quantitative histochemistry of the nervous system by ultramicroanalysis is presented by R. Wayne Albers. A final summarizing chapter by Edward Dempsey concludes a worthwhile little book. Most readers will appreciate the arrangement of a single bibliography for all the references.

A. R. V.

Selected Writings of Walter E. Dandy

Compiled by C. E. Troland and F. J. Otenasek. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 789 pages. $15.00.

AMERICAN NEUROSURGERY, to a large extent, has been founded upon the pioneering works of Harvey Cushing and Walter Dandy. Because the outstanding contributions of Walter Dandy were published in many different journals, both American and foreign, neurosurgeons will be grateful to Drs. Troland and Otenasek who have compiled his major papers, unabridged, in a single volume.

In this series of 78 articles published from 1911 to 1946 are papers on many subjects which interested Dandy, from the blood supply of the pituitary gland to the seat of consciousness. Included in their number are many "firsts" – ventriculography, total extirpation of acoustic neuromas, posterior route for trigeminal section, hemispherectomy, partial eighth nerve section for Ménière's syndrome, and intracranial clipping of aneurysms, among others. There is also the description of the herniated intervertebral disk – with the speculation that such lesions might offer a pathologic explanation for sciatica.

The reviewer regrets that the compilers did not add a biographic foreword regarding this rugged and skilful pioneer in neurologic surgery. Such a sketch would have been welcomed by all who have admired his accomplishments in the field.

From the practical standpoint, the book is attractive and well printed. More complete and uniform bibliographic references would have appealed to literary stylists, and a subject index would have greatly added to the usefulness of the compilations. However, these collected papers can be recommended to all interested in the development of neurologic concepts and neurosurgical technics for the alleviation of diseases of the nervous system.

A. E. W.

Oligophrenia in Combination with Congenital Ichthyosis and Spastic Disorders. A clinical and genetic study.

Torsten Sjögren and Tage Larsson. Acta Psychiat. et Neurol. Supplementum 113, Vol. 32. 1957. Copenhagen: Ejnar Munksgaard. 25 Swedish crowns.

SJÖGREN AND LARSSON describe a syndrome consisting of oligophrenia, congenital ichthyosis, spastic paraplegia, and, less consistently, degenerative retinitis. The syndrome is genetically determined through a monohybrid, autosomal, recessive type of transmission of the heritable trait. This was traced in 33 individuals of 11 families, all stemming from a geographically restricted area of a single county in northern Sweden. The genealogic study of the affected families encompassed ten generations extending back to the

seventeenth century. Such research in human pathogenetics is possible probably only in Sweden. The ethnic homogeneity, the stability of communal traditions and practices, and the relative constancy of ecologic conditions through three centuries of uninterrupted political and economic peace make of Sweden a unique observatory of human genetics.

The new heredofamilial syndrome appears to have a well substantiated claim for being a genuine clinical and genic entity. In the 33 affected individuals the instances of dissociated or abortive forms of this syndrome were remarkably few. The perimacular retinal degeneration was more frequently wanting than any other of the four cardinal components of the syndrome; the ophthalmologic examination which was available in 14 cases revealed retinal degeneration in three. Oligophrenia was not demonstrable in three. The spasticity was absent or not noted in five. Early mortality among individuals affected with this congenital syndrome was high; the life span was half of that for the general population; yet in several instances the hereditary affection was compatible with survival to the early sixties, the oldest patient being 64. There was a high incidence of consanguinity in the genealogic trees of affected families.

The new syndrome is of distinct interest and should be known especially to workers in the field of mental deficiency. The occurrence of this syndrome in the institutions for feeble-minded persons in Sweden was estimated to be 1:1000. Theoretically, one might expect a similar incidence of this syndrome among feeble-minded persons in other countries. The density of distribution of mutant gene, however, may vary greatly in different populations. Its apparent concentration in a small geographic zone of a county in Sweden appears to be the corollary of the historical-cultural factors lacking in most other parts of man's living space on this planet. This monograph is a significant contribution to human genetics and its pathology.

P. I. Y.

The Significance of Electroencephalography for the Diagnosis and Localization of Cerebral Tumors

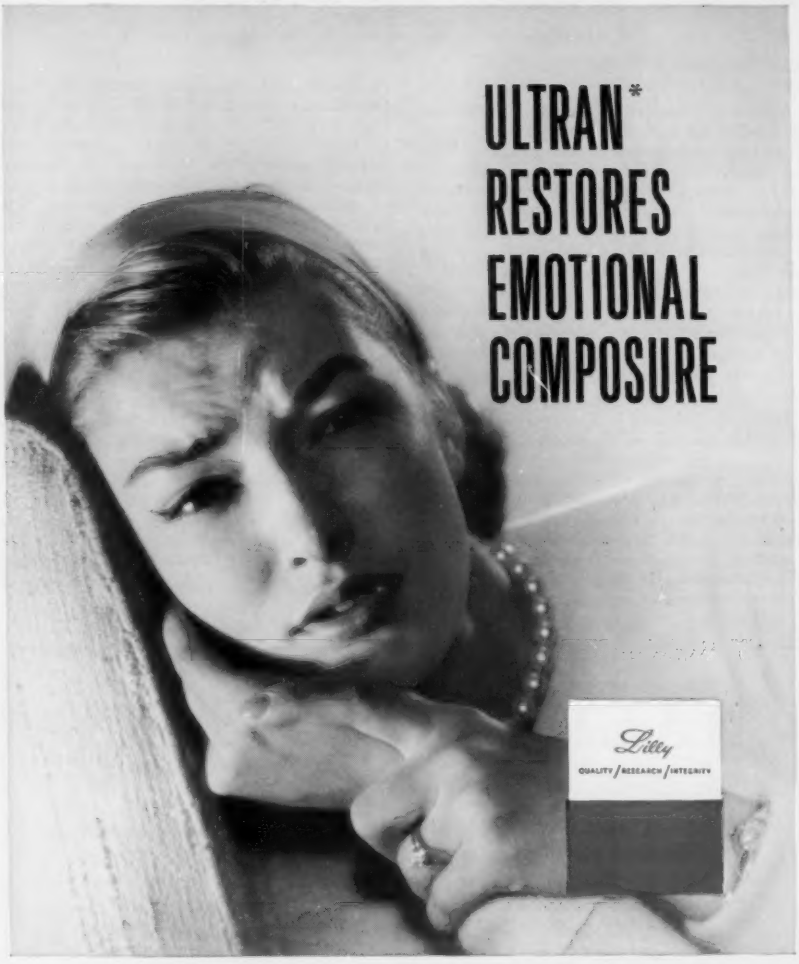
J. H. A. Van Der Drift. 1957. Leiden: H. E. Stenfert Kroese N. V. 131 pages.

THIS IS A WELL BALANCED STUDY based on 344 cases of cerebral tumor verified at operation or autopsy, presented with reference to electroencephalographic findings and with due consideration for other clinical modes of examination. The book, printed in Holland, is written in English; it contains summaries in Dutch, French, and German. It is well illustrated; the series of 12 drawings presenting the actual localization of tumor as compared with the site of maximum delta activity is especially worthy of commendation.

The author studied in detail electroencephalographic abnormalities caused by different types of tumors and was not able to find a pattern specific for each histologic type.

The methodology is within the range of standard procedure. No strikingly original observations are made, but the value of electroencephalography as an important and sometimes critical accessory in the diagnosis of brain tumor is demonstrated by a straightforward analysis of an extensive series of cases. Electroencephalographically-minded clinicians will find this work worth reading.

A. B. V.



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JANUARY 1958

Special Review Courses to Precede AAN Meeting

The traditional two-day prelude to the annual Academy meetings are the special review courses in clinical and basic neurology, organized by the AAN committee on special courses, of which A. B. Baker is chairman. This year the course in neuropathology, an annual "must," will be repeated. Other courses previously given will appear in new form and some completely new courses will be introduced. Each course, whether previously given or not, will present new advances in its respective field. Among the courses to be given are: disorders of movement, under Charles A. Kane; EEG, under Frank Morrell; pediatric neurology, under Sidney Carter; neuro-ophthalmology, under N. S. Schlezinger; and neuropathology, under Fae Y. Tichy. There is to be a new course in neuropharmacology, chaired by Donald B. Tower, which will present the pharmacology of neuronal conduction and of tranquilizing and related drugs. Other considerations will be the pharmacologic aspects of treatment of cerebrovascular disease and of the reactions of the nervous system to various toxic agents. Another new course will cover the fine structure of the nervous system, under the chairmanship of William F. Windle. This course will include the microscopic and chemical structure of neurons, the fine structure of neurons, neuroglia, the central neuropil, and the fine structure of synapse. Also included in the course will be consideration of the fine structure of myelin in the peripheral and central nervous system. Joe R. Brown will again give his popular course on current advances in neurology in revised form. The special review courses will precede (April 21-23) the annual AAN meeting at the Bellevue-Stratford Hotel in Philadelphia (April 24-26).... Except for neuropathology, the fee for each course will be $15.00 for junior members; $20.00 for fellows, actives, and associates; and $30.00 for non-members. The course in neuropathology requires, in addition to the regular fee, a deposit of $25.00 for the loan of slides which will be refunded when the slides are returned. This fee is the same for all membership categories.... Since enrollment in these courses will be limited, early registration is urged. Application forms and other information may be obtained from Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 3501 East 54th Street, Minneapolis 17, Minnesota.

Postgraduate Course in Clinical Neurology

Under the direction of Russell N. DeJong, a postgraduate course in clinical neurology will be given at the University Hospital, Ann Arbor (May 7-8, 1958). Inquiries and communications should be addressed to the Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

Epilepsy Program Emphasizes Treatment

At the scientific sessions of the annual meeting of the American League Against Epilepsy, Hotel Roosevelt, New York (Dec. 12, 1957), a scientific program was presented, highlighting treatment and management. Included in the sessions were papers on toxic reactions to anticonvulsant drugs and their control; physiologic and EEG, clinical and therapeutic aspects of status epilepticus; and the medical and psychologic aspects of psychomotor and temporal lobe epilepsy. A. J. Derbyshire and A. L. Rolfe of Detroit made a presentation on "A Mobile EEG Laboratory Serving Convulsive Patients." The presidential address was given by J. K. Merlis. A. E. Walker reported on the International League meeting, held in conjunction with the International Congress of Neurological Sciences, Brussels, July 1957. Gilbert H. Glaser was chairman of the scientific program, while Dr. William Caveness was in charge of local arrangements.

Eastman Lauds Symposium on Kernicterus

Nicholson J. Eastman, president of the American Academy for Cerebral Palsy and professor of obstetrics and gynecology at Johns Hopkins University School of Medicine, praised highly the symposium on "The Role of Erythroblastosis and Kernicterus in Cerebral Palsy," held on the day preceding (Nov. 24) the eleventh annual meeting of the American Academy for Cerebral Palsy in the Hotel Roosevelt, New Orleans (Newsletter, Dec. 1957). Prof. Eastman said: "The real highlight of our meeting was the symposium on kernicterus, which attracted the largest attendance of any of the scientific sessions. New work was reported and discussed with pertinent vigor. A prominent guest discussor was J. Godwin Greenfield of London, now a visiting scientist at the National Institute of Neurological Diseases and Blindness, who pioneered the original neuropathologic studies on the basal ganglia in neonatal jaundice." Professor Eastman went on to say, "this symposium was in keeping with the policy of the Academy to consider neurologic basic research as an essential additive to its sessions on cerebral palsy." .... The symposium on kernicterus was prepared by the AACP research committee, comprising Chester A. Swinyard, chairman, Pearce Bailey, Webb E. Haymaker, and H. Houston Merritt.

Easter Seal Foundation Makes Research Awards

At its October 29 meeting in Chicago, the Easter Seal Research Foundation of the National Society for Crippled Children and Adults, under its chairman, Dr. William T. Sanger, Chancellor of

the Medical College of Virginia, awarded 12 grants, including renewals, in the amount of $81,770.67. Among the AAN members to receive awards were Francis M. Forster, Isabel Lockard, and Meyer A. Perlstein.... Since the first meeting of the foundation's board of trustees in October 1956, 22 grants totaling $183,178.28 for research studies have been made to institutions and scientists from coast to coast--to universities, medical schools, and professional organizations. The foundation's research program is a comprehensive one, seeking to expand both basic and clinical research in every phase of crippling.... Inquiries should be addressed to Dr. William Gellman, Director, Easter Seal Research Foundation, National Society for Crippled Children and Adults, 11 South LaSalle Street, Chicago 3, Illinois.

Scientific Counselors Appointed at NINDB A group of six experts have been appointed as scientific counselors to advise in the conduct of the basic and clinical investigations programs at the National Institute of Neurological Diseases and Blindness in Bethesda. Members of the group are: Hallowell Davis (St. Louis) chairman, Raymond D. Adams (Boston), Howard Curtis (Upton, N. Y.), Algernon B. Reese (New York), R. J. Rossiter (London, Canada), and A. Earl Walker (Baltimore). It is planned that this advisory group will hold about two meetings a year at NINDB.... The establishment of advisory groups on intramural programs at the National Institutes of Health followed a recommendation of a committee appointed by the National Science Foundation in 1955 at the request of the Department of Health, Education, and Welfare.

Neurosurgeons Meet in Washington The Congress of Neurological Surgeons held the seventh annual meeting at the Statler Hotel, Washington, D. C. (Dec. 8-9). The program featured a symposium on pediatric neurology. The principal guest speaker was Francis C. Grant of Philadelphia.

Construction Started on Muscle Institute On an L-shaped plot of 27,500 square feet extending from East 71st to 72nd Streets, New York City, ground-breaking ceremonies for construction of the Institute for Muscle Disease of the Muscular Dystrophy Associations of America were conducted (Oct. 18). MDAA President William Mazer introduced the participants: Mr. Paul Cohen, chairman MDAA Executive Committee; Dr. A. T. Milhorat, chairman MDAA Medical Advisory Committee; Mrs. Robert F. Wagner, wife of New York City's mayor; Johnny Power, a muscular dystrophy patient; and Mrs. Lou Gehrig, national campaign chairman.... The Institute for Muscle Disease, scheduled to open in December 1958, is to be a center for research in muscular dystrophy and related disorders and serve as a clearing-house for the collection and dissemination of data in this field gathered from all over the

world. The center, according to MDAA spokesmen, will in no way curtail the associations' established program of research grants .... Included on the board of trustees of the Muscle Institute are Detlev W. Bronk, president of the Rockefeller Institute for Medical Research, and Cornelius P. Rhoads, director of the Sloan-Kettering Institute and scientific director of the Memorial Center for Cancer and Allied Diseases.

Briefs Herbert H. Jasper, professor of experimental neurology, McGill University, Montreal, gave the annual Israel S. Wechsler lecture (Dec. 13, 1957), at the Mount Sinai Hospital in New York. His topic was progress and problems in brain research.... Dr. John Meyer has been appointed head of the newly formed department of neurology at Wayne State University in Detroit.... In a recent issue of MEDICINE AND HYGIENE, Professor M. Minkowski (Zurich) has an interesting article on his impressions of neurology and psychiatry gathered during a recent trip to the United States. His impressions were developed as a result of visits to New York, Boston, Baltimore, Washington, Bethesda, Richmond, Galveston, and Atlantic City where he attended the 1957 meeting of the American Neurological Association and was made an honorary member. His visit was made possible through a senior fellowship from the University of Texas School of Medicine in Galveston.... This year's Gold Medal Award by the University of Rochester Medical School Alumni Association went to Paul Garvey.... Recently has come the sad news of the death of AAN fellow R. Finley Gayle, Jr., of Richmond, Va. (Nov. 4, 1957).... A recent visitor to the New York Neurological Institute was Peter Bradshaw of the University of Leeds, England.... J. L. O'Leary has been added to the NINDB Advisory Council.... The National Institute of Mental Health has established a technical information unit and psychopharmacology service center in Bethesda, to stimulate and facilitate research in this field and serve as a general clearing-house for psychopharmacologic information. Dr. Lorraine Bouthilet heads this unit.

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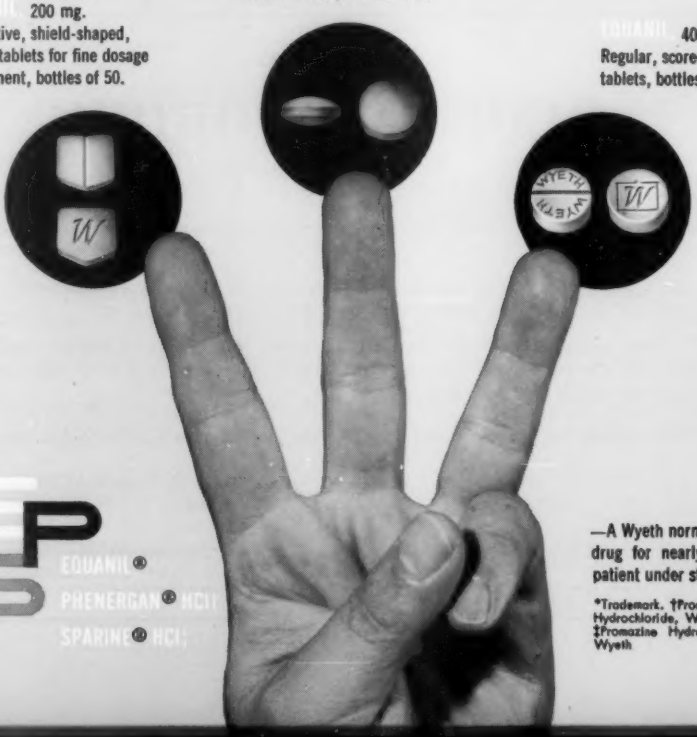

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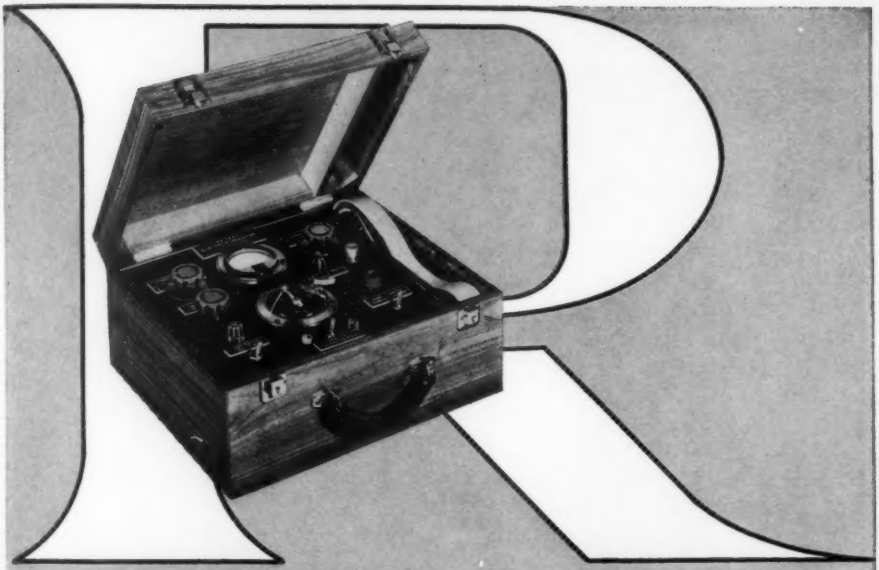

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